IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 21, Issue 8 Ser.1 (August. 2022), PP 06-11
www.iosrjournals.org

"Comparison Two Different Doses of Intravenous Ondansetron with Placebo on Attenuation of Spinal-Induced Hypotension"

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Abstract
Background:*Spinal anesthesia is a simple, reliable, and most common anesthetic technique practiced worldwide. Hemodynamic instability is most common intraoperative complication after spinal anesthesia during cesarean delivery. Spinal anesthesia causes bradycardia and hypotension via activation of Bezold-Jarisch reflex. Ondansetron is specific 5- HT3 receptor antagonist that alleviates the Bezold-Jarisch reflex lead to decrease hypotension and bradycardia.Despite the popularity and ease of its use, this procedure is frequently associated with hemodynamic instability.* ***Objective:*** *To compare the effect of different doses of intravenous ondansetron with placebo on attenuation of spinal-induced hypotension.****Methods****: A Prospective Randomised Interventional Study was carried out at Dept. of Anaesthesiology, Netrokona Medical College and Hospital, Netrokona, Bangladesh from January to June 2022. 110 patients belonging to ASA class-I and II, aged 25- 35 years, weight 40-60 kilograms, undergoing cesarean delivery under spinal anesthesia were included in this study. Randomization was done by chit in box method. Patients were assigned into ondansetron group (group A, n=55) or the normal saline group (group B, n=55) to receive either ondansetron 6mg diluted in normal saline (total volume made 10 ml) intravenously or 10ml normal saline intravenous respectively.Blood pressure and heart rate were checked every 5minutes till the end of the surgery. Data was analyzed by chi square test.* ***Results:****In our study 110 patients were investigated for the effect of prophylactic ondansetron 6mg intravenously on fall in SBP, DBP and MBP, number of vasopressor boluses and total dose of vasopressor required. The effect of ondansetron on the level of sensory height, duration of subarachnoid block to start of surgery, duration of surgery, heart rate, incidence of nausea, shivering and bradycardia.Systolic, diastolic and mean blood pressure were found to be higher in group A as compare to group B at different time intervals (P value <0.05). In group A 67% patients required vasopressors whereas in group B 91% patients required vasopressors. Incidence of nausea and vomiting is less in group A (P value=0.001).* ***Conclusion:****In conclude that prophylactic use of intravenous ondansetron prevent incidence of hypotension and less vasopressor is required to treat hypotension. Prophylactic intravenous ondansetron causes reduced incidence of hypotension, requirement of vasopressors and Post-operative nausea-vomiting during spinal anaesthesia.*

Keywords:*Ondensetron, Hypotensiòn, Spinal Anesthesia, Bupivacaine.*

Date of Submission: 21-07-2022 Date of Acceptance: 05-08-2022

I. Introduction

Spinal anesthesia is one of the common methods of providing anesthesia for various surgeries. Despite the popularity and ease of its use, this procedure is frequently associated with hemodynamic instability. Spinal anesthesia is a simple, reliable, and most common anesthetic technique practiced worldwide [1,2]. However, spinal anesthesia is associated with side effects such as hypotension, bradycardia, and shivering [3,4]. The

incidence of hypotension and bradycardia in non-obstetric patients has been reported to be 33% and 13%, respectively. In obstetric, non-laboring patients, the incidence of hypotension has been estimated to be as high as 50–60%; this is less common after the onset of labor [5,6]. Probably reduction in vascular resistance by sympathetic nerve blockade is the main reason of hypotension.Hypotension is most common intraoperative complication during spinal anaesthesia for caesarean section which has detrimental effects on both mother and fetus[7]. Hypotension during spinal anesthesia results from combined effect of reduced cardiac output and decreased vascular tone caused by sympathetic blockade; aortocaval compression by the gravid uterus; activation of Bezold-Jarisch reflex and increased venous capacitance secondary to the pooling of blood in the lower extremities and abdomen[8]. The responsible receptors for the BJR are mechanoreceptors located in the heart walls which participate in systemic responses to hyper and hypovolemia. They also include chemoreceptors sensitive to serotonin (5-HT3 receptors) [9].BJR has been activated by decreased venous return, pain, stress or fear. BJR is also activated during regional anaesthesia, hemorrhage or supine inferior vena cava compression in pregnancy by paradoxical activation of various non-cardiac baroreceptors. Activation of BJR receptors causes increases parasympathetic nervous system activity and inhibits sympathetic activity which causes a rapid fall in blood pressure and heart rate in association with apnea [10]. A number of strategies are commonly used to prevent hypotension include intravenous administration of fluids, avoidance of aorto-caval compression, lateral uterine displacement, trendelenburg or leg rising, compression devices on the legs, prophylactic vasopressors, low-dose spinal anaesthesia or performing a CSEA technique in the left lateral position but none of them is 100% effective [11]. Even though spinal anesthesia is a simple and safe procedure, rare complications such as unresponsive hypotension and bradycardia are real anesthetic challenges. It is preferred to prevent hypotension rather than treating it. Hence, in the recent past, most of the studies are focusing on prophylactic management of hypotension; ondansetron is such a drug gaining popularity in the prevention of hypotension in patients who underwent subarachnoid block.According to null hypothesis (H0) there was no significant difference in effect of ondansetron and placebo on spinal induced hypotension. According to alternate hypothesis (H1) there is significant difference in effect of ondansetron on spinal induced hypotension as compared to placebo.

II. Material And Methods

A Prospective Randomised Interventional Study was carried out at Dept. of Anaesthesiology, Netrokona Medical College and Hospital, Netrokona, Bangladesh from January to June 2022.110 patients belonging to ASA class-I and II, aged 25-35 years, weight 40-60 kilograms, undergoing cesarean delivery under spinal anesthesia were included in this study. Randomization was done by chit in box method. Patients were assigned into ondansetron group (group A, n=55) or the normal saline group (group B, n=55) to receive either ondansetron 6mg diluted in normal saline (total volume made 10 ml) intravenously or 10ml normal saline intravenous respectively. An anesthesia resident, who was not part of the study, administered drug to all patients intravenously 10minutes before spinal anesthesia. Neither patient nor the observer was aware of the type of medications given to patient.Patient with history of PIH, convulsion, compromised airway or morbid obesity and required general anaesthesia for supplementation were excluded from study. The required sample size was 60 in each group at 95% confidence and 80% power to verify the expected difference of 17% in patients who develop hypotension with ondansetron 6mg (0.01%) in comparison with placebo (17%).Intravenous cannulation was done by 18G cannula and ringer lactate was started. Study solution was infused intravenously 10 minutes before spinal anaesthesia. After 10 minutes under strict aseptic conditions lumbar puncture was performed in lateral decubitus position at L3-L4 or L4- L5 interspace in midline approach via 25G quincke needle and 10mg (2ml) 0.5% hyperbaric bupivacaine was given in subarachnoid space. After the injection patient was turned supine immediately. Oxygen 4.0 L/min was given by ventury mask to the patients. Vitals were checked every 5 minutes till the end of the surgery. Shivering was treated by injection tramadol 100mg intravenously. Other adverse effect (if any) in peri-operative period were noted and treated accordingly. If patient needed more sedation during surgery, 1mg midazolam intravenously was given.Statistical analysis was done using SPSS software version 20 and p value < 0.05 was considered to be significant.

III. Results

In our study 110 patients were investigated for the effect of prophylactic ondansetron 6mg intravenously on fall in SBP, DBP and MBP, number of vasopressor boluses and total dose of vasopressor required. The effect of ondansetron on the level of sensory height, duration of subarachnoid block to start of surgery, duration of surgery, heart rate, incidence of nausea, shivering and bradycardia.Table 1 shows that distribution of cases according to age was comparable (p=0.339) in both groups (ondansetron group -26.27±3.62 and normal saline group -25.63±3.60). In both groups maximum patients was below 25 yrs. old.Table 2, 3 and 4 shows that systolic blood pressure, diastolic blood pressure and mean blood pressure were found to be higher in ondansetron group as compare to normal saline group at different time intervals ($P<0.05$). Fall in systolic,

diastolic and mean blood pressure as compared to baseline blood pressure was significantly less in ondansetron group as compared to the normal saline group.Total dose of vasopressor required in ondansetron group (4.67 ± 6.31) was found to be less than normal saline group (9.80±7.24) (p=0.001). In ondansetron group 27 patients required vasopressors whereas in normal saline group 51 patients required vasopressors (fig-1).Nausea was found to be less in ondansetron group than normal saline group (p=0.001). Incidence of shivering was not found significantly different in both groups (p=0.500). Incidence of bradycardia was found same in both groups (fig-2). Distribution of cases according to the level of sensory height, onset of adequate sensory block and duration of surgery was not significantly different in both groups.

Table 1: Distribution of cases according to age group in both groups (N=110)

Age Group	Ondansetron Group		Normal Saline Group		Total		P value
	No.	%	No.	%	No.	%	
≤25	29	52.7	38	69.0	67	60.9	
26-35	23	41.8	12	21.8	35	31.8	
>35	3	5.4	5	9.0	8	7.2	**0.339**
Total	55	100	55	100	110	100	
Mean±SD	26.27±3.62		25.63±3.6				

Table 2: Statistical comparison of systolic blood pressure (mmHg) at difference time intervals in both groups (N=110)

Time Intervals (min)	Ondansetron Group		Normal SalineGroup		P value
	Mean	SD	Mean	SD	
Basal	126.9	10.93	127.46	9.85	0.766
0	123.83	12.64	126.83	8.41	0.129
5	116.23	14.35	100.61	17.96	0.001
10	115.5	17.35	110.23	16.5	0.091
20	113.43	15.07	106.8	13.76	0.013
30	114.01	14.14	110.35	13.58	0.154
40	116.5	9.94	109.74	9.98	0.007
50	120.83	7.11	119.12	11.24	0.751

Table 3: Statistical comparison of diastolic blood pressure (mmHg) at difference time intervals in both groups (N=110)

Time Intervals (min)	Ondansetron Group		Normal SalineGroup		P value
	Mean	SD	Mean	SD	
Basal	82.08	9.19	82.27	7.42	0.905
0	80.15	9.88	82.63	7.41	0.122
5	72.66	13.7	61.13	12.53	0.001
10	71.86	14.02	66.63	13.47	0.039
20	68.45	11.03	62.35	11.98	0.004
30	68.31	12.63	65.11	15.29	0.22
40	71.93	9.11	63.4	9.49	0.001
50	71.83	8.08	73.37	6.28	0.694

Table 4: Statistical comparison of mean arterial pressure (mmHg) at difference time intervals in both groups (N=110)

Time Intervals (min)	Ondansetron Group		Normal SalineGroup		P
	Mean	SD	Mean	SD	
Basal	96.88	8.97	97.35	7.33	0.756
0	94.76	9.77	97.16	6.87	0.122
5	87.21	13.29	74.38	13.82	0.001

10	85.63	13.66	81.38	13.7	0.092
20	84.51	11.03	77.41	12.4	0.001
30	83.39	12.12	79.41	12.33	0.08
40	86.96	8.41	78.62	9.21	0.001
50	86.83	7.08	88.75	6.94	0.621

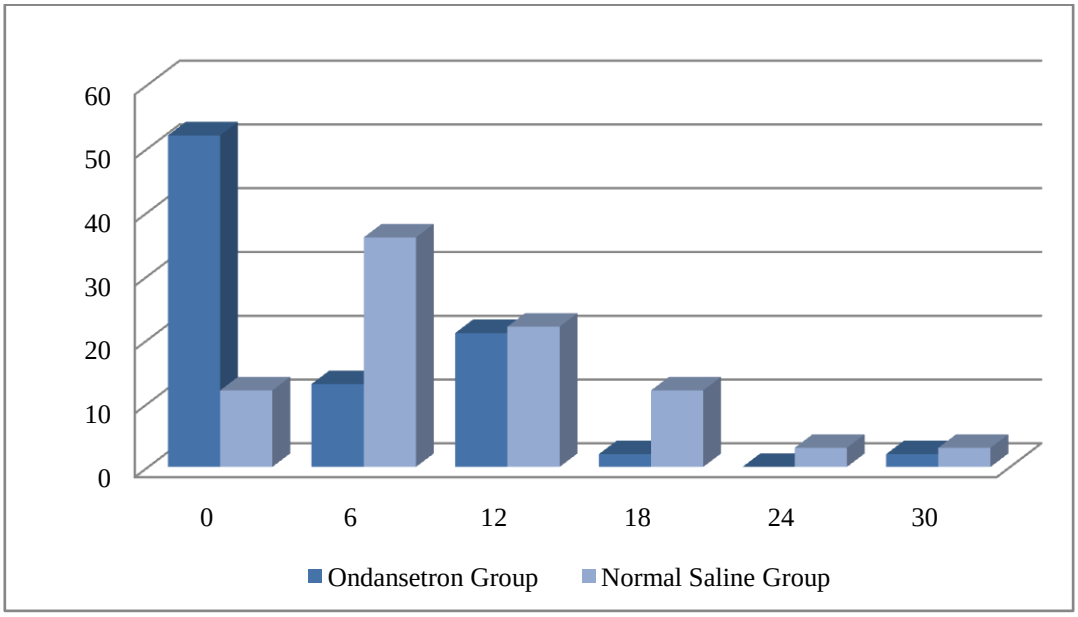

Figure 1: Distribution of cases according to total dose of vasopressor required in both groups.

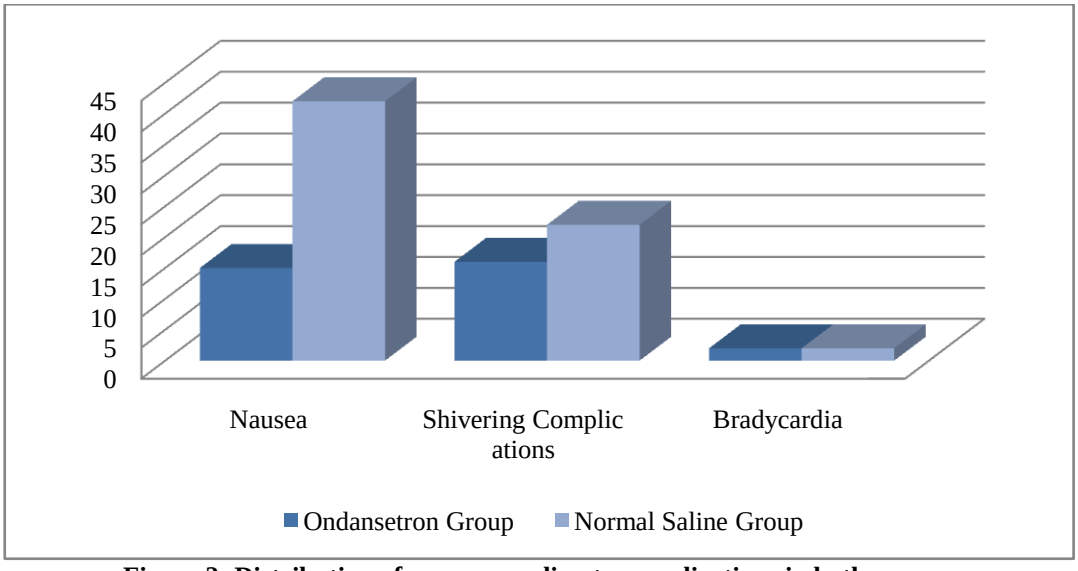

Figure 2: Distribution of cases according to complications in both groups.

IV. Discussion

This study demonstrated that administration of two different doses of intravenous ondansetron attenuates spinal induced hypotension. Hypotension during spinal anesthesia is a common side effect of this procedure, whereas bradycardia occurs rarely. Hemodynamic changes usually are benign; however, in selected patients, they may lead to serious consequences, including cardiac arrest, though it is a consequence of progressive bradycardia rather than progressive hypotension [4-6].Maternal hypotension after spinal anesthesia for caesarean delivery occurs because of activation of bezoldjarish reflex. Ondansetron is a specific 5-HT_3 receptor antagonist. It is highly effective to alleviate the Bezold-Jarisch reflex (BJR) and thus prevent hypotension to occur.We observed that hypotension occurred in significantly fewer patients in the ondansetron group 27 patients (45%) as compared to those in the normal saline group 53 patients (85%). Fall in SBP, DBP and MBP was significantly less in ondansetron group as compared to normal saline group. Similarly, Marashi

SM et al., [12] demonstrated that ondansetron 6mg and 12mg group patients had less incidence of hypotension as compared to the normal saline group (P 0.04). Meng Wang et al., [13] demonstrated that incidence of maternal hypotension was significantly less in group Andansetron 4mg and ondansetron 6mg group ($p<0.05$ as compared to normal saline group. Wang Q et al.,[14] demonstrated that maternal hypotension was less in ondansetron 4mg treated patients. WalidTrabelsi et al., [15] demonstrated that hypotension occurred in 37.5% patients in ondansetron 4mg group as compared to 77.5% patients in normal saline group ($p<0.001$).Similarly,Sahoo T et al. [16] demonstrated that patient in ondansetron 4mg group needed less vasopressor than normal saline group ($p=0.009$). Marashi SM et al.,[12] demonstrated that vasopressor required in ondansetron 6 and 12mg groups were less as compare to normal saline group (P 0.04). Meng Wang et al.,[13] demonstrated that consumption of phenylephrine in ondansetron 4mg group was significantly less than that in normal saline group ($p<0.05$). Wang Q et al.,[14] demonstrated that need of phenylephrine in ondansetron 4mg group was less ($p= 0.029$). WalidTrabelsi et al.,[15] demonstrated that the average consumption of ephedrine intraoperative in ondansetron 4mg group was 5.10±7.78 while in normal saline group was 12.90±9.24 ($p<0.001$). Nivatpumin P et al., [17] demonstrated that the proportion of ondansetron 8mg group patients requiring norepinephrine was significantly lower than in placebo group ($p=0.02$).We observed that mean heart rate was not significantly different in both groups ($p>0.05$) throughout the surgery. In our study we observed that total dose of vasopressor required in ondansetron group 4.67±6.31 was significantly less in the Ondansetron group as compared to normal saline group 9.80±7.24 ($p=0.001$).Similarly,Owczuk R et al., [18] demonstrated that heart rate values were not significantly different between ondansetron 8mg group and placebo group. Meng Wang et al.,[13]demonstrated that the means of maternal HR after spinal anesthesia were not affected in ondansetron 2, 4 and 8mg group, but were dramatically increased in group A ondansetron 6mg group B. Owczuk et al.[18] demonstrated that heart rate was not significantly different in both groups. Incidence of nausea and vomiting was less in ondansetron group as compared to normal saline group was attributed to antiemetic effect of ondansetron. Vagus nerve activates the vomiting center in medulla oblongata. Ondansetron reduce the activity of vagus nerve and block serotonin receptors in chemoreceptor trigger zone results in decreased nausea and vomiting. WalidTrabelsi et al. [15] demonstrated that 22.5% patients in ondansetron 4mg group experienced nausea vomiting as compared to 62.5% patients in normal saline group ($p<0.001$).We observed that shivering occurred in the Ondansetron group in 11 patients which was not significantly different as compared to those in the normal saline group 14 patients ($p=0.50$). Ram Bhakta Koju et al., [19] demonstrated that the incidence of postoperative nausea was less in ondansetron 4mg group (8%) as compare to normal saline group (56%) ($p< 0.001$).In our study, the height of sensory block, onset of sub arachnoid block and the duration of surgery were not significantly different between the normal saline group and the ondansetron group ($p>0.05$). Similarly in previous studies done by Browning, R. Met al., [20] also found that the height of sensory block, onset of subarachnoid block and the duration of surgery were comparable in both the normal saline group and the ondansetron group.

V. Conclusion

In conclude that prophylactic use of intravenous ondansetron prevent incidence of hypotension and less vasopressor is required to treat hypotension. Prophylactic intravenous ondansetron causes reduced incidence of hypotension, requirement of vasopressors and Post-operative nausea-vomiting during spinal anaesthesia.

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Pranab Kumar Debnath, et. al. "Comparison Two Different Doses of Intravenous Ondansetron With Placebo on Attenuation of Spinal-induced Hypotension."*IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 21(08), 2022, pp. 06-11.