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Research Article

Different Doses of Intravenous Ondansetron With Placebo on Attenuation of Spinal-induced Hypotension

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ABSTRACT

Introduction: Spinal anesthesia is a simple, reliable, and most common anesthetic technique practiced worldwide. However, spinal anesthesia is associated with side effects such as hypotension, bradycardia, and shivering. Hypotension is most common intraoperative complication during spinal anaesthesia for caesarean section which has detrimental effects on both mother and fetus. **Objective**: To compare the effect of intravenous ondansetron with placebo for attenuation of spinal induced hypotension, change in heart rate, requirement for vasopressor and incidence of shivering and postoperative nausea- vomiting. **Methods**: A prospective randomised double blind study was conducted at Department of Anesthesia, Monno Medical College & Hospital, Manikganj, Bangladesh from July to December 2022. Total 100 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. Group O (n=50) received 6mg ondansetron in normal saline intravenously; total volume made 10ml. Group S (n=50) received 10ml normal saline intravenously. Patient with history of PIH, convulsion, compromised airway or morbid obesity and required general anaesthesia for supplementation were excluded from study. Blood pressure and heart rate were checked every 5minutes till the end of the surgery. Data was analyzed by chi square test. **Results**: Total 100 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. Distribution of cases according to age was comparable (p-0.339) in both groups (ondansetron group-25.27±3.62 and normal saline group-24.63±3.60). In both groups maximum patients were below 25yrs old. We also studied 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 O as compare to group S at different time intervals (p value < 0.05). In group O 66% patients required vasopressors whereas in group S 90% patients required vasopressors. Incidence of nausea and vomiting is less in group O (p-value=0.001). **Conclusion**: we conclude that prophylactic use of intravenous ondansetron prevent incidence of hypotension and less vasopressor is required to treat hypotension. Prophylactic ondansetron use is associated with less incidence of nausea and vomiting in spinal anesthesia in healthy parturient.

Key Words: *Hypotensiòn, Ondensetron, Spinal Anesthesia, Bupivacaine.*

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INTRODUCTION

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 mechanism involved in the occurrence of hypotension is decrease in vascular resistance caused by sympathetic blockade which in turn causes vasodilatation and finally leads to drop in arterial pressure [5,6]. Hypotension is most common intraoperative complication during spinal anaesthesia for caesarean section which has detrimental effects on both mother and fetus [7,8]. 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 [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]. 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. Spinal induced hypotension (SIH) is caused due to sympathetic blockade resulting in decreased systemic vascular resistance whereas bradycardia occur secondary to parasympathetic dominance, increased baroreceptor activity or activation of Bezold Jarisch reflex (BJR). BJR is a triad of bradycardia, hypotension and peripheral vasodilation which arises from stimulation of mechanoreceptors and chemoreceptors located in the left ventricle [11,12]. Serotonin (5HT) has been found to trigger this reflex in various animal studies in hypovolemic settings [13,14].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 [15]. Vagal chemo sensitive C fibers involved in Bezold–Jarisch reflex activation and they are richly supplied with 5-hydroxytryptamine type 3 (5-HT_3) receptors. 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.

Material & Methods

A prospective randomised double blind study was conducted at Department Of Anesthesia, Monno Medical College & Hospital, Manikganj, Bangladesh from July to December 2022. Total 100 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. Patient with history of PIH, convulsion, compromised airway or morbid obesity and required general anaesthesia for supplementation were excluded from study.

Patients were assigned into ondansetron group (group O, n=50) or the normal saline group (group S, n=50) 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.

In the preoperative ward the anesthetic technique was explained to all patients. A pre-anesthetic checkup was done. After taking informed consent and confirming 8 hours fasting patient was taken on the operation table. Baseline vitals like blood pressure, pulse rate, saturation were recorded. 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 L4L5 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. Table was tilted about 15^0. Oxygen 4.0 L/min was given by ventury mask to the patients. Upper level of block was checked by pinprick method from caudal to rostral direction after 5 minutes and after that every 2 minutes up to adequate level of block (T_6) was achieved. Vitals were checked every 5 minutes till the end of the surgery. Hypotension was defined as a fall in mean arterial pressure greater than 20% from the baseline value or <80 mmHg and treated with incremental doses of injection ephedrine 6 mg intravenously. Bradycardia was defined as fall in heart rate below 50 beats per min and treated with incremental doses of atropine 0.5 mg intravenously. Vomiting was treated by injection metoclopramide 10mg intravenous. 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 21.0 and p value < 0.05 was considered to be significant.

Results

Total 100 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. Table 1 shows distribution of cases according to age was comparable (p-0.339) in both groups (ondansetron group-25.27$\pm$3.62 and normal saline group-24.63$\pm$3.60). In both groups maximum patients was below 25yrs old. We also studied 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 2, 3 and 4 shows 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.

Table 1: Distribution of cases according to age group in both groups (N=100)

Age Group	Ondansetron Group		Normal Saline Group		Total	
	No.	%	No.	%	No.	%
$\leq$25	26	51.7	34	68.0	60	60.0

26-30	21	41.7	10	20.0	31	31.0
>30	3	6.6	6	10.0	09	9.0
Total	50	100	50	100	100	100
Mean	25.27		24.63			
SD	3.62		3.60			
T	0.960					
P	0.339					

Table 2: Statistical comparison of systolic blood pressure (mmHg) at difference time intervals in both groups (N=100)

Time Intervals (min)	No. of Cases (Group O/S)	Ondansetron Group		Normal Saline Group		p-value
		Mean	SD	Mean	SD	
Basal	50/50	126.90	10.93	127.46	9.85	0.766
0	50/50	123.83	12.64	126.83	8.41	0.129
5	50/50	116.23	14.35	100.61	17.96	0.001
10	50/50	115.50	17.35	110.23	16.5	0.091
15	50/50	113.85	16.75	109.11	16.25	0.119
20	50/50	113.43	15.07	106.80	13.76	0.013
25	50/50	111.98	14.75	107.56	13.55	0.090
30	48/50	114.01	14.14	110.35	13.58	0.154
35	40/39	114.38	12.72	110.75	13.65	0.175
40	26/30	116.50	9.94	109.74	9.98	0.007
45	14/18	117.73	9.14	113.68	11.32	0.269
50	5/7	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=100)

Time Intervals (min)	No. of Cases (Group O/S)	Ondansetron Group		Normal Saline Group		p-value
		Mean	SD	Mean	SD	
Basal	50/50	82.08	9.19	82.27	7.42	0.905
0	50/50	80.15	9.88	82.63	7.41	0.122
5	50/50	72.66	13.70	61.13	12.53	0.001
10	50/50	71.86	14.02	66.63	13.47	0.039
15	50/50	69.60	14.10	64.36	12.52	0.034
20	50/50	68.45	11.03	62.35	11.98	0.004
25	50/50	67.80	12.94	62.15	11.48	0.013
30	48/50	68.31	12.63	65.11	15.29	0.220
35	40/39	69.18	11.05	65.14	15.61	0.140
40	26/30	71.93	9.11	63.40	9.49	0.001
45	14/18	75.46	7.33	69.05	7.69	0.019
50	5/7	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=100)

Time Intervals (min)	No. of Cases (Group O/S)	Ondansetron Group		Normal Saline Group		p-value
		Mean	SD	Mean	SD	
Basal	50/50	96.88	8.97	97.35	7.33	0.756
0	50/50	94.76	9.77	97.16	6.87	0.122
5	50/50	87.21	13.29	74.38	13.82	0.001
10	50/50	85.63	13.66	81.38	13.70	0.092
15	50/50	84.43	13.56	79.45	12.75	0.040
20	50/50	84.51	11.03	77.41	12.40	0.001
25	50/50	82.86	13.14	77.51	11.65	0.020
30	48/50	83.39	12.12	79.41	12.33	0.080
35	40/39	84.60	10.73	79.38	12.75	0.030
40	26/30	86.96	8.41	78.62	9.21	0.001

45	14/18	89.46	7.80	83.21	8.64	0.036
50	5/7	86.83	7.08	88.75	6.94	0.621

As figure 1 shows 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 33patients required vasopressors whereas in normal saline group 45 patients required vasopressors.

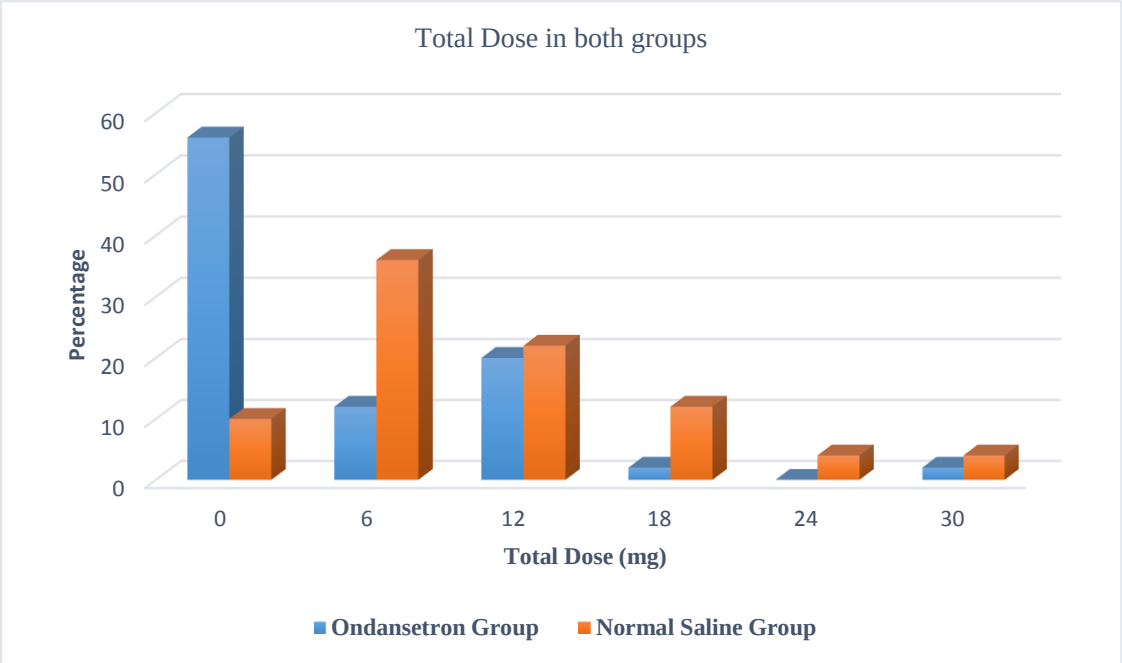

Fig-1: Distribution of cases according to total dose of vasopressor required in both groups

Table-5: Distribution of cases according to complications in both groups.

Complications	Ondansetron N(%)	Normal Saline Group N(%)
Nausea	8-16	20-40
Shivering	9-18	10-20
Brady cardia	0-0.0	0-0.0

We observed that shivering occurred in the Ondansetron group in 09 patients which was not significantly different as compared to those in the normal saline group 10 patients (P 0.50).

DISCUSSION

Hypotension during spinal anaesthesia is a frequently occurring event with incidence up to 33% in non-obstetric population which reaches even higher up to 83% in parturient [16]. It is hazardous for the fetus due to compromise in uteroplacental circulation. So, a number of techniques have been employed for its mitigation [17]. In the background of hypovolemia, cardiac receptors in the left ventricle get stimulated and induce BJR resulting in vasodilation, hypotension and reflex bradycardia. This response is also believed to be encited by chemoreceptors sensitive to serotonin. Ondansetron, a 5-HT3 antagonist has been found to be effective in attenuation of spinal induced hypotension in various studies done in both obstetric and non-obstetric population [18,19]. We have used intravenous ondansetron 4 mg 5 minutes before spinal anaesthesia for elective caesarean section in our study as a measure to prevent hypotension and found it to be effective. 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, Sahoo T et al., [20] demonstrated that patient in ondansetron 4mg group needed less vasopressor than normal saline group (p-0.009). Marashi SM et al., [21] 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., [22] 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., [23] demonstrated that need of phenylephrine in ondansetron 4mg group was less (p-0.029). Walid Trabelsiet al., [28] 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 [24] 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. Similarly, in

2008 Owczuk R et al., [25] demonstrated that heart rate values were not significantly different between ondansetron 8mg group and placebo group. Meng Wang et al., [22] 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 ondansetron 6mg group. Mohammad Reza Safaviet al., [26] demonstrated that incidence of bradycardia was not significantly different in ondansetron 8mg and normal saline group. Terkawi AS et al., [27] demonstrated that heart rate was not significantly different between normal saline group and ondansetron 8mg group (P 0.18). R. Owczuket al., [25] demonstrated that heart rate was not significantly different in both groups. We observed that hypotension occurred in significantly fewer patients in the ondansetron group 33 patients (66%) as compared to those in the normal saline group 45 patients (90%). Fall in SBP, DBP and MBP was significantly less in ondansetron group as compared to normal saline group. Similarly, in 2014, Marashi SM et al., [21] 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., [22] demonstrated that incidence of maternal hypotension was significantly less in group ondansetron 4mg and ondansetron 6mg group (P <0.05 as compared to normal saline group. Wang Q et al [23]in demonstrated that maternal hypotension was less in ondansetron 4mg treated patients. Walid Trabelsiet al., [28] 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). We observed that PONV occurred in significantly fewer patients in the ondansetron group (16.7% patients) as compared to those in the normal saline group (43.3% patients) (p-0.001). Similarly, Sahoo T et al., [20] demonstrated that patient in ondansetron 4mg group had significantly lower incidence of nausea and vomiting (P 0.049). Meng Wang et al., [22] demonstrated that incidence of nausea in ondansetron 2mg, 4mg, 6mg and 8mg groups were significantly less than normal saline group (p<0.05). Wang Q et al., [23] demonstrated that nausea was significantly less in ondansetron 4mg treated patients. Walid Trabelsiet al., [28] 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). Ram Bhakta Kojuet al., [29] 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 Marashi SM et al., [21], Meng Wang et al., [22] and Walid Trabelsiet al., [28] 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 (P >0.05). We observed that shivering occurred in the Ondansetron group in 09 patients which was not significantly different as compared to those in the normal saline group 10 patients (p-0.50). Similarly, in 2013 Browning RM et al., [30] demonstrated that incidence of shivering was not significantly different in ondansetron 8mg group (41%) as compared to normal saline group (47%) (p-0.54). 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.

CONCLUSION

We conclude that prophylactic use of intravenous ondansetron prevent incidence of hypotension and less vasopressor is required to treat hypotension. Prophylactic ondansetron use is associated with less incidence of nausea and vomiting in spinal anesthesia in healthy parturient.

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