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Research Article

A Prospective Randomised Interventional Study of Intravenous Ondansetron With Placebo for Attenuation of Spinal Induced Hypotension

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Abstract: ***Background and Aims:*** 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-HT_3 receptor antagonist that alleviates the Bezold-Jarisch reflex lead to decrease hypotension and bradycardia. The present study was done 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. ***Material and Methods:*** 120 Patients of ASA1/2, age 20-35years, weight 40-60Kgs undergoing cesarean delivery under spinal anesthesia were selected for study. History of PIH, convulsion or allergy to the drug used, requires general anaesthesia for supplementation were excluded from study. Randomization was done by chit in box method. Group O (n=60) received 6mg ondansetron in normal saline intravenously; total volume made 10ml. Group S (n=60) received 10ml normal saline intravenously. Blood pressure and heart rate were checked every 5minutes till the end of the surgery. Data was analyzed by chi square test. ***Results:*** 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 67% patients required vasopressors whereas in group S 91% patients required vasopressors. Incidence of nausea and vomiting is less in group O (P value=0.001). ***Conclusion:*** Prophylactic intravenous ondansetron causes reduced incidence of hypotension, requirement of vasopressors and Post-operative nausea-vomiting during spinal anaesthesia.

Keywords: hypotensiòn, ondensetron, bezold jarisch reflex, spinal anesthesia, bupivacaine.

INTRODUCTION

Hypotension is most common intraoperative complication during spinal anaesthesia for caesarean section which has detrimental effects on both mother and fetus (Bhardwaj, N. *et al.*, 2013; & Romdhani, C. *et al.*, 2014).

Hypotension during spinal anesthesia results from combined effect of reduced cardiac output and decreased vascular tone caused by sympathetic blockade; aorto-caval 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 (Ayorinde, B. T. *et al.*, 2001).

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 (Godlewski, G. *et al.*, 2003).

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 (Rucklidge, M. W. M. *et al.*, 2002).

Vagal chemosensitive C fibers involved in Bezold–Jarisch reflex activation and they are richly supplied with 5-hydroxytryptamine type 3 (5-HT_3) receptors. Thus we aimed to study the use of ondansetron which is a 5 HT_3 receptor antagonist for prevention of hypotension occurring after spinal

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anesthesia in cesarean delivery. Our primary objectives were to compare 2 groups in terms of development of spinal induced hypotension and change in heart rate. Our secondary objectives were to compare 2 groups in terms of requirement for vasopressor, incidence of shivering and incidence of postoperative nausea and vomiting. For this we used null hypothesis and alternate hypothesis. 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 AND METHODS

After Ethical Committee approval (Ref. No.2349 MC/EC/2016) and informed written consent, 120 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. The study was conducted from April 2016 to June 2016. 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 6 mg (0.01%) in comparison with placebo (17%).

The study was a hospital based, randomized, double blind, comparative, interventional study. Randomization was done by chit in box method. Patients were assigned into ondansetron group (group O, n=60) or the normal saline group (group S, n=60) 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 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. 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

In the current study 120 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. 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.

As 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.

Table 1: Distribution of cases according to age group in both groups

Age Group	Ondansetron Group		Normal Saline Group		Total	
	No.	%	No.	%	No.	%
$\leq$25	31	51.7	41	68.3	72	60.0
26-30	25	41.7	13	21.7	38	31.7
>30	4	6.6	6	10.0	10	8.3
Total	60	100	60	100	120	100
Mean	25.27		24.63			

SD	3.62	3.60
T	0.960	
P	0.339	

As 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 2: Statistical comparison of systolic blood pressure (mmHg) at difference time intervals in both groups

Time Intervals (min)	No. of Cases (Group O/S)	Ondansetron Group		Normal Saline Group		T	P
		Mean	SD	Mean	SD		
Basal	60/60	126.90	10.93	127.46	9.85	0.298	0.766
0	60/60	123.83	12.64	126.83	8.41	1.530	0.129
5	60/60	116.23	14.35	100.61	17.96	5.261	0.001
10	60/60	115.50	17.35	110.23	16.5	1.703	0.091
15	60/60	113.85	16.75	109.11	16.25	1.571	0.119
20	60/60	113.43	15.07	106.80	13.76	2.516	0.013
25	60/60	111.98	14.75	107.56	13.55	1.707	0.090
30	58/60	114.01	14.14	110.35	13.58	1.437	0.154
35	50/49	114.38	12.72	110.75	13.65	1.366	0.175
40	32/35	116.50	9.94	109.74	9.98	2.773	0.007
45	15/19	117.73	9.14	113.68	11.32	1.124	0.269
50	6/8	120.83	7.11	119.12	11.24	0.325	0.751

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

Time Intervals (min)	No. of Cases (Group O/S)	Ondansetron Group		Normal Saline Group		T	P
		Mean	SD	Mean	SD		
Basal	60/60	82.08	9.19	82.27	7.42	0.120	0.905
0	60/60	80.15	9.88	82.63	7.41	1.557	0.122
5	60/60	72.66	13.70	61.13	12.53	4.812	0.001
10	60/60	71.86	14.02	66.63	13.47	2.084	0.039
15	60/60	69.60	14.10	64.36	12.52	2.149	0.034
20	60/60	68.45	11.03	62.35	11.98	2.901	0.004
25	60/60	67.80	12.94	62.15	11.48	2.529	0.013
30	58/60	68.31	12.63	65.11	15.29	1.234	0.220
35	50/49	69.18	11.05	65.14	15.61	1.487	0.140
40	32/35	71.93	9.11	63.40	9.49	3.747	0.001
45	15/19	75.46	7.33	69.05	7.69	2.462	0.019
50	6/8	71.83	8.08	73.37	6.28	0.403	0.694

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

Time Intervals (min)	No. of Cases (Group O/S)	Ondansetron Group		Normal Saline Group		T	P
		Mean	SD	Mean	SD		
Basal	60/60	96.88	8.97	97.35	7.33	0.312	0.756
0	60/60	94.76	9.77	97.16	6.87	1.556	0.122
5	60/60	87.21	13.29	74.38	13.82	5.182	0.001
10	60/60	85.63	13.66	81.38	13.70	1.701	0.092
15	60/60	84.43	13.56	79.45	12.75	2.073	0.040
20	60/60	84.51	11.03	77.41	12.40	3.313	0.001
25	60/60	82.86	13.14	77.51	11.65	2.359	0.020
30	58/60	83.39	12.12	79.41	12.33	1.767	0.080
35	50/49	84.60	10.73	79.38	12.75	2.202	0.030
40	32/35	86.96	8.41	78.62	9.21	3.858	0.001
45	15/19	89.46	7.80	83.21	8.64	2.185	0.036
50	6/8	86.83	7.08	88.75	6.94	0.057	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 27 patients required vasopressors whereas in normal saline group 51 patients required vasopressors.

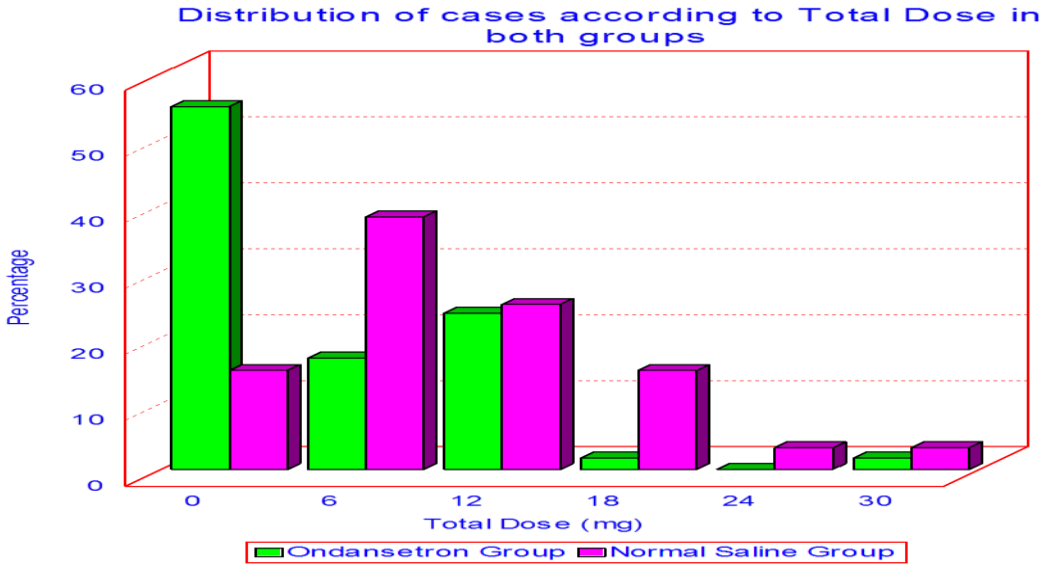

Figure 1: Distribution of cases according to total dose of vasopressor required in both groups

As figure 2 shows 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.

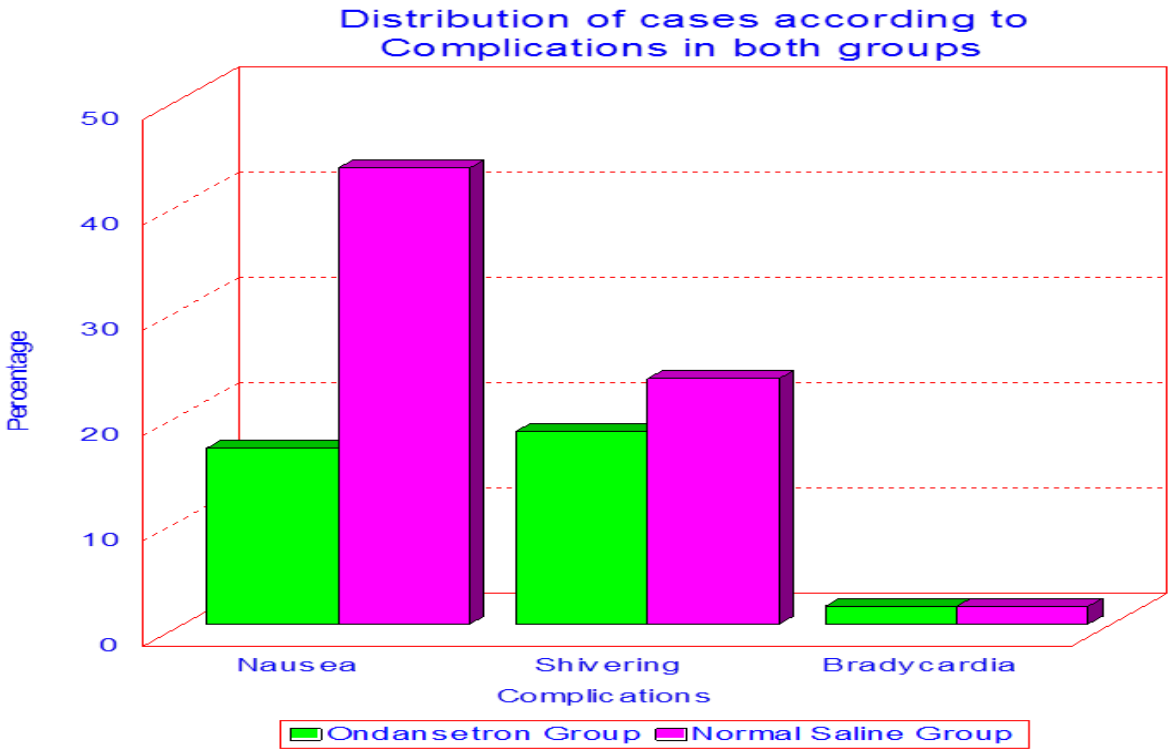

Figure 2: Distribution of cases according to complications in both groups

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.

Maternal hypotension after spinal anesthesia for caesarean delivery occurs because of activation of bezold jarish reflex. Ondansetron is a specific 5-HT_3

DISCUSSION

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 in 2014, Marashi SM *et al.,* 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.,* in 2014 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.,* in 2014 demonstrated that maternal hypotension was less in ondansetron 4mg treated patients. Walid Trabelsi *et al.,* (2015) 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).

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 in 2012 Sahoo T *et al.,* (2012) demonstrated that patient in ondansetron 4mg group needed less vasopressor than normal saline group (P 0.009). Marashi SM *et al.,* (2014) 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.,* (2014) 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.,* (2014) demonstrated that need of phenylephrine in ondansetron 4mg group was less (P 0.029). Walid Trabelsi *et al.,* (2015) 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.,* (2016) 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.,* (2008) demonstrated that heart rate values were not significantly different between ondansetron 8mg group and placebo group. Meng Wang *et al.,.,* (2014) 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. Mohammadreza Safavi *et al.,* (2015) demonstrated that incidence of bradycardia was not significantly different in ondansetron 8mg and normal saline group. Terkawi AS *et al.,* (2015) demonstrated that heart rate was not significantly different between normal saline group and ondansetron 8mg group (P 0.18). R. Owczuk *et al.,.,* (2015) demonstrated that heart rate was not significantly different in both groups.

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 in 2012 Sahoo T *et al.,.,* demonstrated that patient in ondansetron 4mg group had significantly lower incidence of nausea and vomiting (P 0.049). Meng Wang *et al.,.,* (2014) 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.,.,* (2014) demonstrated that nausea was significantly less in ondansetron 4mg treated patients. Walid Trabelsi *et al.,.,* (2015) 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 Koju *et al.,* (2015) demonstrated that the incidence of postoperative nausea was less in ondansetron 4mg group (8%) as compare to normal saline group (56%) (P < 0.001).

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.

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). Similarly in 2013 Browning RM *et al.,* (2013) demonstrated that incidence of shivering was not significantly different in ondansetron 8mg group (41%) as compared to normal saline group (47%) (P 0.54).

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.,* (2014), Meng Wang *et al.,* (2014) and Walid Trabelsi *et al.,* (2015) 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).

CONCLUSION

Hence, we can 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.

Prudence dictates that its use needs further evaluation for it to gain widespread acceptance.

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