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Ondansetron Attenuates Hypotension Due To Subarachnoid Block-A Randomised Double Blind, Placebo-Controlled Study

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ABSTRACT

Background: A decrease in arterial blood pressure is one of the known complications of subarachnoid block (SAB) and represents a major cause of concern in some patients. Improvements in surgical and anaesthetic techniques have not helped to curb the incidence of hypotension. Therefore search is going on for various modalities to decrease the incidence.
Aim: To test the hypothesis that ondansetron attenuates the arterial hypotension and bradycardia produced due to subarachnoid block.
Methods: A randomised double blind, placebo-controlled study was performed on 60 patients. They were divided into two groups. Group O patients received 8 mg ondansetron in 10 ml of isotonic NaCl intravenously before SAB. Group P patients had received isotonic NaCl solution 10 ml intravenously without any added medication before SAB. The systolic (SBP), diastolic (DBP) and mean arterial pressure (MAP) and heart rate (HR) were recorded every 5 minutes for first 20 minutes and every 10 Minutes up to 40 minutes. After the subarachnoid block in both groups and subjected to statistical analysis. The Statistical analysis was performed by STATA 11.1 (College Station TX USA). Students paired t-test was used to assess the significance difference between the pre and post comparisons of heart rate and blood pressures. Continuous variables were expressed as mean and standard deviation; Categorical variables were expressed as frequency and percentage. P<0.05 considered as statistically significance.
Results: It was noted that the systolic and diastolic and mean arterial blood pressure fall was less in ondasetron group while comparing to the placebo group. The ondansetron group and the placebo group patients did not have significant effect on heart rate induced by SAB.
Conclusion: The attenuation of fall in blood pressure during subarachnoid block can be achieved with ondansetron given intravenously before SAB.

Key words: Ondansetron, Subarachnoid block, Arterial blood pressure drop, Bradycardia, Surgical procedures

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INTRODUCTION

Subarachnoid block (SAB) is an efficient method of providing intra-operative analgesia and is a safe alternative to general anaesthesia in many surgical interventions. Despite its numerous advantages, SAB is not without adverse effects, which include unwarranted cardiovascular events. In most cases, these include arterial hypotension and bradycardia, the incidence of which is estimated to reach 33% and13%, respectively, in the non-obstetric population [1,2]. Blockade of sympathetic nerves causes reduction in vascular resistance and a decrease in arterial pressure. Bradycardia is related to relative dominance of the parasympathetic system, increased baroreceptor activity, or to the Bezold-Jarisch reflex (BJR) [1]. The latter is triggered by stimulation of intracardiac receptors, and its consequences include Bradycardia, vasodilatation, and hypotension [3]. Receptors triggering the Bezold-Jarisch reflex 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) [4]. 5-HT3 receptors vary from other serotonin receptors, which are mainly coupled to G-protein. They are ligand-gated, fast ion (Na+/K+) channels [5], and activation of the receptors by serotonin or other ligands (phenylbiguanide or 2-methyl-5-HT) results in increased efferent vagal nerve activity [6].

It seems that both types of receptors are involved in the induction of hypotension andbradycardia after subarachnoid blockade. Although mechanoreceptors located in all cardiac chambers are normally sensitive to distension, diminished venous return of blood, as observed after subarachnoid block, induces deformation of the cardiac wall, resulting in irritation of mechanoreceptors and activation of the Bezold- Jarisch reflex. Chemoreceptors are activated by serotonin released from activated thrombocytes [7,8]. Animal studies suggest that serotonin may be an important factor inducing BJR in cases of decreased blood volume [7,9,10], and the mechanism of triggering the reflex depends on activation of peripheral 5-HT3 receptors located in intracardiac vagal nerve endings by serotonin [11]. Yamano et al. demonstrated that 5-HT3 receptor blockade antagonizes BJR induced by serotonin administration in rats [12]. The aim of the present study was to verify the hypothesis that blockade of type 3 serotonin. Receptors by intravenous ondansetron administration would reduce hypotension and bradycardia induced by subarachnoid block.

MATERIALS AND METHODS

This study was conducted in ASA class I and II patients of both sex aged between 20-70 years undergoing various surgical procedures under SAB. During the period of Aug 2018-Dec 2020. The exclusion criteria included : patient's refusal, hypersensitivity to ondansetron, history of allergy to local anaesthetic agents, patients with arterial hypertension, coronary heart disease, cardiovascular insufficiency, on anti-hypertensive agents, selective serotonin reuptake inhibitors or serotonin-related migraine medication, patients on coagulation abnormalities were excluded from the study.Heart rates, non-invasive blood pressure, mean arterial pressure, pulse oximetry, respiratory rate, electro cardiogram were the parameters observed in this study. After Ethical committee approval, fulfilment of inclusion and exclusion criteria and taking informed written consent from patient, the study was conducted as follows. Patients were randomly allocated to either in the ondansetron group (O) and in the placebo (P) group (30 in each group) using sealed envelope technique. A routine preoperative assessment was made on the previous day. Patients were fasted for 10 hrs before anaesthesia and no pre-loading was done before the procedure. Patients were pre medicated 60 mins before anaesthesia with oral midazolam 7.5mg. In the operation theatre the above said monitors were connected, base line values recorded for heart rate, non-invasive blood pressure (Systolic BP, Diastolic BP, Mean arterial pressure). 18 G Intravenous cannula was inserted for I.V. fluid and drug administration. I.V. slow (0.9%) NaCl was started during study period so as not to exceed 200 ml during the entire study period.

I.V. 8 mg ondansetron in 10 ml of isotonic NaCl was given (for ondansetron group) intravenously 5 minutes prior to the performance of the Subarachnoid block. A 3 ml of 0.5% hyperbaric bupivacaine solution was given intrathecally in L3- L4/L4-L5 space by 25/26/27 G QB spinal needle.

I.V. Isotonic NaCl solution 10 ml was given for the placebo group intravenously 5 minutes prior to the performance of the subarachnoid block. A 3 ml of 0.5% hyperbaric bupivacine solution was given intrathecally in L3- L4/L4-L5 space by 25/26/27 G QB spinal needle.

From this moment onwards the level of anaesthesia was evaluated every five minutes till the study period. The person administering the solution was unaware of the content in the syringe.

Heart rate and non-invasive blood pressure values were recorded for every 5 minutes for the 20 minutes and every 10 minutes up to 40 minutes after the SAB and both the groups we compared with the base line values and after Subarachnoid block values.

Surgical procedure including, patient positioning, tourniquet placement and urinary catheterization were not done during study period.

Lumbar puncture was performed with the patient in a sitting position, and the subarachnoid space was punctured at the L3-L4 or L4-L5 level.

quicke babcok spinal needle 25-, 26-, or 27-gauge needles were used. After identification of the subarachnoid space (cerebrospinal fluid outflow), 3 mL of 0.5% hyperbaric bupivacaine solution (Spinal 0.5% Heavy; AstraZeneca) was administered. Immediately after completing the subarachnoid injection, patients were positioned supine on the operating table. From this moment on, the level of anesthesia was evaluated 4 times (every 5 minutes) with cold sensation (using alcohol swab).

At the same time points, the level of motor blockade was assessed (according to the Bromage scale: 0, no paralysis; 1, inability to lift the thigh [only able to move kneeand feet]; 2, inability to flex the knee [only able to move feet]; 3, inability to move any joint in the legs), and heart rate and arterial pressure were measured. Atropine (0.5 mg intravenously) was administered in cases of bradycardia, and ephedrine (10 mg intravenously) in cases of hypotension, respectively. Medication was individually decided upon by the anesthesiologist participating in the operation.

Blockade distribution (number of anesthetized segments above S1) is presented in Figure 1. Numbers of anesthetized segments at respective time points did not differ between the groups. Blockade level increased until the 15-minute time point; statistically significant differences were observed between the levels of analgesia after 5 minutes and at the following evaluation time points, but there were no such differences after 5, 10, 15, 20, 30 and 40 minutes of blockade.

Bromage scores of motor block showed no significant differences between the groups at the respective time points. Motor blockade only at level 2 or 3 was noted after 5, 10, 15, 20, 30 and 40 minutes in both groups.

Statistical methods

The Statistical analysis was performed by STATA 11.1 (College Station TX USA). Student-test were performed to assess the significance difference between the age, height, weight, BMI, level of spinal blockade, blood pressure and heart rate with the groups. Students paired t-test was used to assess the significance difference between the pre and post comparisons of heart rate and blood pressures. Continuous variables were expressed as mean and standard deviation; Categorical variables wereexpressed as frequency and percentage. P<0.05 considered as statistically significance.

RESULTS AND OBSERVATIONS

Demographic parameters did not differ significantly. (p> 0.05) for all comparisons. Patient demographic and anthropometric details of the patients are shown in table 1

Table 1: Demographic Data (Mean+/_SD)

	Ondansetron Group	Placebo Group	P-Value
	(n=30)	(n=30)	
	Mean ± SD	Mean ± SD	
Age	32.8 ± 9.9	34.8 ± 11.8	0.481
Weight	65.8 ± 9.35	63.53 ± 8.1	0.326
Height	158.17 ± 6.6	155.6 ± 9.18	0.214
BMI	26.3 ± 3.5	26.19 ± 2.38	0.932
Body Mass Index			
Normal	11 (37%)	11 (37%)	
Overweight	14 (17%)	18 (3%)	0.085
Obese	5 (47%)	1 (60%)	
Gender			
Male	29 (97%)	25 (83%)	0.085
Female	1 (3%)	5 (17%)	
Type of Surgery Performed			
Hernia Surgery	9 (30%)	14 (47%)	
Excision of Sac	7 (23%)	7 (23%)	0.064*
PerinealSurgeries	3 (10%	6 (20%)	
ORIF	5 (17%)	3 (10%)	
Others	6 (20%)	--	

*Fisher Exact test,ORIF-Open Reduction and internal Fixation All numbers are mean

P value < 0.05 significant

Most of the patients in the study were males. 29 of 30 cases and 25 of 30 control patients were males. Only 1 case was female and 5 controls were females as shown in table.

Most of the patients were overweight (53.3%) followed by normal (36.7 %) and obese patients (10%) as shown in table 3 of distribution of BMI among patients.Larger percentage of patients were from hernia surgeries (38.3%) as this is the most common group of surgery performed under spinal anaesthesia. Rest was followed by excision of sac forming single most common surgery done. Perineal surgery and ORIF were other surgeries done. Distribution of patients according to type of surgery is shown in Table 2.

Table 2: Characteristics of the Motor Blockade

	Ondansetron	Placebo	P-Value
5 Minutes			
Bromage 3	5	10	0.136
Bromage <3	25	20	
10 Minutes			

Bromage 3	18	12	0.196
Bromage <3	12	18	
15 Minutes			
Bromage 3	20	22	0.779
Bromage <3	10	8	
20 Minutes			
Bromage 3	25	24	1.000
Bromage <3	5	6	
30 Minutes			
Bromage 3	26	25	1.000
Bromage <3	4	5	
40 Minutes			
Bromage 3	26	25	1.000
Bromage <3	4	5	

As shown in table 2, The progress of intensity of motor block after 5 minuites of SAB,10 min, 15,20,30and 40 min after SAB was similar in both study groups- group-O and group P.It was found to bestatically not significant. (P>0.05)

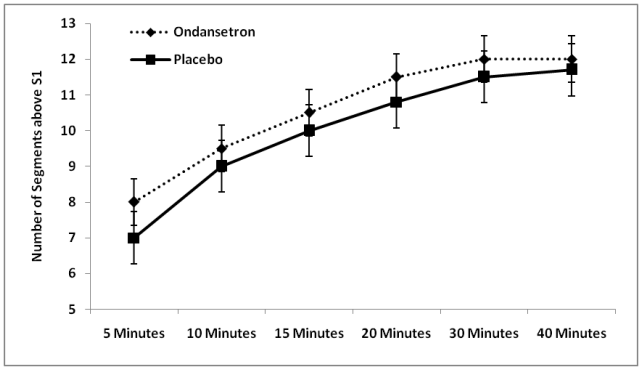

Figure 1: Blockade distribution (number of anesthetized segments above S1) : Means and 95% Confidence interval.

As shown in figure 1 the height of motor block achieved after SAB was similar in both study groups at 5,10,15,20,30 and 40 min.it was fond to be statistically not significant(P>0.05).

HR, SBP, DBP, MAP at 5 minutes and baseline for both placebo and ondansetron group are compared in table 3.

Table 3: Hemodynamic Changes (expressed as Mean ± SD)

	Ondansetron Group (n=30)		**Placebo Group (n=30)**		**P-Value**
	Mean ± SD	**P-Value**	**Mean ± SD**	**P-Value**	**P-Value***
Heart Rate (bpm)					
Baseline	78.1 ± 16.8		79.97 ± 13.47		0.636
5 Minutes	77.67 ± 15.8	0.604	78.53 ± 13.64	0.256	0.821
10 Minutes	75.97 ± 14.3	0.801	75.17 ± 15.36	0.015	0.835
15 Minutes	76.8 ± 15.7	0.245	77.6 ± 15.29	0.169	0.849
20 Minutes	77.07 ± 17.8	0.475	77.01 ± 15.82	0.144	1
30 Minutes	77.50 ± 15.8	0.55	79.42 ± 16.2	0.898	0.459
40 Minutes	77.8 ± 15.2	703	78.5 ± 16.3	0.689	0.259
Systolic Blood Pressure (mmHg)					
Baseline	115.3 ± 8.8		116.3 ± 8.8		0.662
5 Minutes	112.2 ± 9.57	<0.001	112.03 ± 10.98	<0.001	0.001
10 Minutes	112.9 ± 13.8	0.204	109.3 ± 9.75	<0.001	0.248

15 Minutes	110.37 ± 9.29	<0.001	102.37 ± 8.29	<0.001	0.001
20 Minutes	110.17 ± 10.72	<0.001	94.17 ± 11.39	<0.001	<0.001
30 Minutes	111.4 ± 8.9	<0.001	92.4 ± 8.8	<0.001	<0.001
40 Minutes	110.5 ± 9.5	<0.001	90.5 ± 8.5	<0.001	<0.001
Diastolic Blood Pressure (mmHg)					
Baseline	75.3 ± 8.21		76.20 ± 9.6		0.698
5 Minutes	70.6 ± 8.6	<0.001	76.6 ± 8.02	0.001	0.002
10 Minutes	69.73 ± 8.89	<0.001	66.1 ± 9.5	<0.001	0.131
15 Minutes	67.97 ± 8.39	<0.001	62.6 ± 8.13	<0.001	0.019
20 Minutes	68.2 ± 7.84	<0.001	58.47 ± 8.9	<0.001	<0.001
30 Minutes	68.7 ± 6.28	<0.001	57.89 ± 9.34	<0.001	<0.001
40 Minutes	68.32 ± 4.30 <0.001 56.57 ±8.80 <0.001	<0.001	56.57 ±8.80	<0.001	<0.001
Mean Arterial Blood Pressure (mmHg)					
Baseline	87.47 ± 7.73		88.23 ± 11.56		0.766
5 Minutes	83.7 ± 8.73		87.47 ± 9.05	0.69	0.005
10 Minutes	83 ± 9.24	0.001	78.60 ± 8.35	<0.001	0.058
15 Minutes	80.77 ± 8.77	<0.001	74.30 ± 8.23	<0.001	0.005
20 Minutes	83.63 ± 10.85	<0.001	69.83 ± 9.03	<0.001	<0.001
30 Minutes	83.24 ± 9.20	<0.001	67.35 ± 8.60	<0.001	<0.001
40 Minutes	83.13 ± 8.50	<0.001	65.88 ± 7.50	<0.001	<0.001
*Between the group Comparisons. P-Value – Intra Group Comparisons					

All values are mean

P value < 0.05 significant

The fall in heart rate was not significant between the two groups with p >0.05 as there was no clinically discernable difference in attenuation of heart rate in case group as compared to control group. The fall in systolic and diastolic BP was significantly attenuated in case group when compared to control group with their base line values in the first 5 minutes. The systolic BP reduction was significantly attenuated in case group with p= 0.001. The reduction in diastolic BP was attenuated in case group with p= 0.002. Mean arterial pressure fall was significantly attenuated with p= 0.005 in the case group.

The heart rate, systolic BP, diastolic BP and mean arterial pressure at 10, 15 and 20 minute intervals were compared with their baseline values for both placebo and ondansetron group and shown in table.

All values are mean P value < 0.05 significant

The attenuation in fall of Heart rate was not significant with p=0.84

The attenuation in fall of systolic BP was not significant in study group at 10 minute interval with p=0.24, but significant at 15 and 20 minutes with p <0.05.

Comparison of the heart rate at baseline, 5, 10, 15 and 20 minute showed no significant changes in case and control group when compared to their baseline values as depicted. Changes in the heart rate 5th, 10th, 15th and 20th minute. No significant changes seen between case and control group. The attenuation in fall of heart rate was not significant with p=0.84.Attenuation of fall in systolic blood pressure was significant in case group when compared to control group with the respective base line values, except at 10 min interval P (0.001 to <0.001).

Changes in the SBP at 5th, 10th, 15th and 20th minute.

P value < 0.005 (except at 10 minutes).The attenuation in fall of SBP was not significant in study group at 10 minute interval with p=0.24, but significant at 15 and 20 minutes with p <0.05.Fall in the diastolic blood pressure at 5th, 10th, 15th and 20th minute. Comparison of DBP between case and control group as compared to their baseline studies. Fall in the DBP at 5th, 10th, 15th and 20th minute P value < 0.05 (except at 10 minutes)

Comparison of diastolic blood pressure between case and control group as compared to their baseline studies showed significant attenuation of BP fall (p< 0.05) except at 10 min (p=0.13).

Mean arterial pressure among case and control group, shows significant attenuation of BP fall in case group (p

<0.05) showing the effect of ondansetron in attenuation of BP fall by spinal anaesthesia to be significant when compared to placebo. Changes in the Mean Arterial Pressure at 5th, 10th, 15th and 20th minute

P value < 0.05

DISCUSSION

The major finding in the present study is the observation of decreased fall in the systolic, diastolic and mean blood pressures in patients who were given 8 mg intravenous ondansetron before SAB, as compared to those patients who received placebo. Fall in arterial pressure accompanying subarachnoid blockade is a common side effect. Hemodynamic changes due to SAB are generally benign; however, occasionally, they may lead to serious complications, including cardiac arrest. Moreover, hypotension is not desirable in patients with ischemic heart disease or those with cerebrovascular insufficiency. It is worth noting that the mechanisms of hypotension in SAB may be different than those producing severe Bradycardia and cardiac arrest. Hypotension is due to a decrease in systemic vascular resistance and filling pressure, due to sympathetic blockade and redistribution of blood in the intravascular compartments. Bradycardia is due to the consequence of Bezold- Jarisch reflex and activation of baroreceptor reflex. It is al so likely that parasympathetic predominance may produce hypotension and bradycardia [13-15]. To combat the cardiovascular side effects of SAB, the following methods are recommended preloading with intravenous fluid infusion, use of vasoconstrictors,head-downposition and administration of anti-cholinergic drug such as atropine [16-18]. There are reports which suggest the cardiovascular side effect of SAB result from stimulation of 5-HT3 receptors in vagal nerve endings [19-26]. This study was aimed to look at the influence of pre-treatment with ondansetron on the incidence of hypotension caused by SAB. Martinek described a case of cardiac arrest in asystole during SAB, which was successfully treated with intravenous ondansetron and atropine [7]. Tsikouris et al. found that granisetron, a 5-HT3 receptor blocker, diminishes heart rate fluctuations occurring during the course of the head-up tilt table test, which might be related to the BJR. In the present study, ondansetron was effective in attenuating hypotension due to SAB; this effect was evident on SAP, DAP and MAP and did not result in significant changes in HR.. Serotonin is known to influence systolic activity of the heart, but through the binding to 5-HT4 receptors [27]. Blauw et al. showed in healthy volunteers, that infusion of serotonin in to the radial artery was associated with vasodilatation and this effect was inhibited by 5-HT3 antagonists, (tropisetron) [28-30]. Current indication for use of serotonin receptor blockers include prevention and in the treatment of post-operative nausea and vomiting [31], and for prevention of shivering in patients undergoing SAB [32]. In this report, how have concluded that pre-treatment with ondansetron decreases the extent of hypotension (SBP, DBP and MAP) Owczuk, et al demonstrated that the use of ondansetron did not have any impact on DAP, but our study demonstrated the maintenance of all the three SBP, DBP and MAP after subarachnoid blockade [33,3 4].

CONCLUSION

We recommend that ondansetron 8mg IV can be administered before spinal anaesthesia to attenuate hypotension. More studies regarding role of 5 HT3 receptors in maintaining of blood pressure should be conducted. Mechanism of Bezold Jarisch reflex has to be studied further. Ondansetron can be used for its antiemetic effect during anaesthesia to prevent aspiration. Ondansetron can be made as a part of protocol during spinal anaesthesia in patients precluding fluid overload.

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