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ORIGINAL ARTICLE

Use of Ondansetron for Prevention of Spinal Induced Hypotension

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ABSTRACT

Objective: To compare the efficacy of prophylactic administration of Ondansetron before induction of spinal anesthesia with placebo, in preventing spinal induced hypotension.

Patients and Methods: This Randomized Control trial was carried out at Holy Family Hospital, Rawalpindi from 29 April 2015 till 28 October 2015. A total of 106 patients were enrolled in the study. Patients in group A, received 6 mg Ondansetron. Patients in group B received normal saline. Mean arterial pressure (MAP) and heart rate (HR) were recorded every 5 minutes after performing spinal anesthesia. The study drug was considered efficacious if absence of hypotension for 20 minutes was recorded after inducing spinal anaesthesia. Data was analyzed using SPSS 17.

Results: Hypotension occurred in 7.5% cases in Ondansetron group compared to 28.3% in normal saline group (p=0.005).

Conclusion: Ondansetron is effective in preventing spinal induced hypotension.

Key words: Bupivacaine, Hypotension, Ondansetron, Spinal Anaesthesia.

Author`s Contribution
[1] *Conception, synthesis, planning of research and manuscript writing*
[2] *Interpretation and discussion*
[3] *Data analysis, interpretation*
[4,5] *manuscript writing, Active participation in data collection*

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Introduction

Spinal anesthesia remains a popular method of anesthesia for a wide range of surgeries due to its efficacy, simplicity, safety, advent of newer drugs with reduced side effects and more benefits for certain patient populations.[1] Its numerous advantages include blockade of the surgical stress response, decreased intraoperative blood loss and transfusion requirements, lower incidence of venous thromboembolism and reduced morbidity and mortality in high-risk patients.[2] However, it is also frequently associated with undesirable effects such as hypotension, bradycardia, and shivering.[3] Hypotension is the most common side effect of spinal anesthesia with a reported incidence as high as 33% in non-obstetric and 60% in obstetric, non-laboring patients.**Error! Bookmark not defined.** Sympathectomy induced decreased systemic vascular resistance and reduced preload secondary to vasodilatation in the lower body are the major mechanisms for this hypotension.[3] Relative dominance of parasympathetic system, activation of Bezold Jarish reflex (BJR) and increased baroreceptor activity are also contributory factors.**Error! Bookmark not defined.** In the setting of decreased blood volume, serotonin may be an important factor inducing the Bezold Jarisch reflex via 5-HT3 receptors located in intracardiac

vagal nerve endings, leading to bradycardia and hypotension.[5] Hemodynamic changes after spinal block are usually benign, but they may lead to serious consequences such as myocardial ischemia and increased stroke risk in certain population groups.[6] In caesarean sections, hypotension results in decreased uteroplacental blood flow, detrimental effects on the fetus and maternal nausea vomiting.**Error! Bookmark not defined.** Various strategies employed to prevent spinal-induced hypotension include fluid preloading and co-loading, prophylactic administration of vasopressors e.g. epinephrine, Trendelenburg positioning, use of lower dose of bupivacaine for subarachnoid block.**Error! Bookmark not defined.** Administering fluids, vasopressors and anticholinergics for the treatment and prevention of hypotension and bradycardia can result in fluid overload, hypertension and tachycardia, which may be poorly tolerated in elderly and coronary artery disease patients.[7] Furthermore, administration of vasoconstrictors may have adverse effects on uterine blood flow in pregnant women. Ondansetron, a selective 5-hydroxytryptamine3 (5-HT3) receptor antagonist, is an effective antiemetic drug used for the prevention and treatment of chemotherapy induced, intraoperative and postoperative nausea and vomiting.[8] Prophylactic administration of Ondansetron has been reported to have a perioperative anti-shivering effect in patients under anesthesia. Recently, it has also been demonstrated to be effective in preventing spinal induced hypotension in multiple studies, possibly by preventing serotonin-induced Bezold-Jarisch reflex (BJR), suppressing venodilatation and augmenting venous return.[9]

In a study conducted in Iran by Marashi et al, 12 (17%) patients in the control group had MAP (Mean arterial pressure) < 80 mm Hg and required vasopressors compared to 0 patients in Ondansetron groups. (P = 0.04).[3] Owczuk R. et al demonstrated that the minimum diastolic and mean blood pressure values obtained over a 20-minute observation period after spinal anesthesia were significantly higher in the Ondansetron group compared to the control group.[9] However, none of these studies has been conducted in Pakistan. The basic aim of our study was to look for the effect of prophylactic Ondansetron administration on spinal induced hypotension in our population, so that Ondansetron if found to be effective, may be routinely used for the prevention of hypotension after spinal anesthesia in elective surgeries.

Patients and Methods

This Randomized Control trial was carried out at Holy Family Hospital, Rawalpindi from 29 April 2015 till 28 October, 2015. A total of 106 admitted elective patients were included in the study. American society of anesthesiologist's classification I and II between the ages of 20-50 years who presented for elective urologic, orthopedic or gynecologic surgeries were included in the study. Exclusion criteria included, patient refusal or any contraindications to spinal anesthesia, any allergy to Ondansetron or local anesthetics and comorbid conditions like hypertension, coronary artery disease or other cardiovascular diseases, diabetes mellitus, pulmonary, hepatic or renal diseases. Patients receiving selective serotonin reuptake inhibitors or migraine medications or obesity BMI >35 were also excluded from the study.

After obtaining approval from hospital ethical committee and written informed consent, patients were recruited according to selection criteria. All patients were assessed a day before surgery for anesthesia fitness. Patients were prepared by fasting (8 h for solid foods, 4 hours for clear fluids). Patients were randomly divided into two equal groups (Group A and Group B) by computer-generated random numbers. On arrival to the operating room, standard monitor was applied to all patients, including pulse oximeter, electrocardiogram and noninvasive arterial blood pressure. Oxygen was delivered via a Venturi facemask at a rate of 4 L/min. An 18-gauge intravenous catheter was placed and patients received 5 ml/kg lactated Ringer solution over 15 minutes before spinal Anesthesia. Then patients in Group-A was given 6 mg Ondansetron diluted in normal saline to 20 ml. The patients in the control group (Group-B) received 20 ml normal saline. In both groups, solutions were infused over 5 minutes just before performing spinal anesthesia. All solutions were prepared by a resident of anesthesiology who was not involved in patient's management or data collection. Baseline parameters (including heart rate, MAP) were recorded 5 minutes prior to induction of spinal anesthesia. Subarachnoid block was performed in the lateral position with a 25-gauge needle inserted by midline approach into the L3-4 interspace. After ensuring the correct position of the needle, 15 mg of 0.75% hyperbaric

bupivacaine was injected. Patients were immediately placed in the supine position after spinal block. The upper level of sensory blockade was evaluated by pinprick test from caudal to rostral direction at 5-min intervals up to 20 minutes. MAP and HR were recorded every 5 minutes up to 20 minutes by an anesthesiologist blinded to the study groups. If MAP dropped <80 mm Hg or decreased more than 20% from baseline, 50 micrograms intravenous Phenylephrine was given, and repeated if necessary. Significant bradycardia (heart rate < 50 beats/min) accompanied by hypotension was treated with 0.5 mg of intravenous Atropine.

Data was collected on a standardized performa and analyzed using SPSS version 17. Mean±SD was calculated for quantitative variables like age, weight, BMI, and MAP. Qualitative variables like gender and hypotension were expressed as frequencies and percentages. Chi-square test was used to compare the incidence of hypotension in the two groups. Effect modifiers like age, gender and indication for surgery were controlled by stratification. Post stratification Chi -Square test was applied. p value <0.05 was considered statistically significant.

Results

Demographic characteristics of both group have been given in table 1. Hypotension occurred in 17.92% patients in our study. In the Ondansetron group, hypotension was observed in 7.5% of cases. In the normal saline group, 28.3% of patients had hypotension.

Table 1: Comparison of demographic characters between two groups (n=106)

Variables	Ondansetron group (n=53)	Placebo group (n=53)	p-value
Age (Years); mean±SD	34.45 ± 1.24	34.98 ± 0.96	0.10
Weight (kg); mean±SD	65.15 ± 1.37	72.58 ± 1.20	0.16
BMI (kg/m^2); mean±SD	23.99 ± 0.44	25.97 ± 0.48	0.48
Gender; n (%) Male Female	27(44) 26(58)	34(56) 19(42)	0.16

Frequency of hypotension was significantly lower in the Ondansetron group as compared to placebo group (Table 2). There was no significant difference in the MAP of both groups at all times (table 3). Regarding gender, among females' frequency of hypotension was lower in the Ondansetron group as compared to placebo but the difference was not statistically significant among males (Table 4).

Table 2: Frequency of hypotension between Ondansetron and placebo groups

Groups	Hypertension				
	Yes		No		p-value
	n	n(%)	n	n(%)	
Ondansetron	4	7.5	49	92.5	.005
Placebo	15	28.3	38	71.7	

Table 3: Mean Arterial Pressure in Ondansetron and Placebo groups

Variable	Ondansetron group (n=53) mean±SD	Placebo group (n=53) mean±SD	p-value
MAP at Baseline (5 minutes before spinal anesthesia)	106.28 ± 0.98	104.54 ± .96	0.94
MAP 5 minutes after spinal Anesthesia	97.77 ± 0.94	93.17 ± 1.44	0.08
MAP 10 minutes after spinal anesthesia	93.77 ± 0.94	89.51 ± 1.28	0.20
MAP 15 minutes after spinal anesthesia	90.26 ± 0.81	85.92 ± 1.15	0.31
MAP 20 minutes after spinal anesthesia	86.74 ± 0.75	82.17 ± 0.99	0.07

Table 4: Comparison of hypotension between Ondansetron and placebo groups stratified by gender (n=106)

Gender	Groups	Hypotension		p-value
		Yes n(%)	No n(%)	
Male	Ondansetron Group (n=27)	2(7)	25(93)	0.09
	Placebo Group (n=34)	8(24)	26(76)	
Female	Ondansetron Group (n=26)	2(8)	24(92)	0.02
	Placebo Group (n=19)	7(37)	12(63)	

There was statistically significant difference in the frequency of hypotension between Ondansetron and placebo groups in urologic surgeries, but the difference between the two groups was insignificant in orthopedic and gynecologic surgeries (Table 5). Difference in frequency of hypotension was also statistically significant between Ondansetron and placebo groups in patients belonging to 20-40 years of age, but the difference was insignificant in age group 41-50 years (Table 6).

Table 5: Comparison of hypotension between Ondansetron and placebo groups stratified by indication for surgery (n=106)

Indications for Surgery	Groups	Hypotension		p-value
		Yes n(%)	No n(%)	
Orthopedic	Ondansetron Group (n=22)	2(9)	20(91)	0.06
	Placebo Group (n=22)	7(32)	15(68)	
Urologic	Ondansetron Group (n=20)	0(0)	20(100)	0.03
	Placebo Group (n=20)	4(20)	16(80)	
Gynaecologic	Ondansetron Group (n=11)	2(18)	9(82)	0.34
	Placebo Group(n=11)	4(36)	7(64)	

Table 6: Comparison of hypotension between Ondansetron and placebo groups stratified by age of patients

Age groups (years)	Groups	Hypotension		p-value
		Yes n(%)	No n(%)	
20 – 30	Ondansetron Group (n=19)	0(0)	19(100)	0.012
	Placebo Group (n=14)	4(29)	10(71)	
31 – 40	Ondansetron Group (n=19)	1(5)	18(95)	0.029
	Placebo Group (n=25)	8(32)	17(68)	
41 – 50	Ondansetron Group (n=15)	3(20)	12(80)	0.924
	Placebo Group (n=14)	3(21)	11(79)	

Discussion

It is frequently observed that spinal anesthesia produces hemodynamic effects. The most frequent of these is hypotension and bradycardia. Hypotension occurs as a result of vasodilatation secondary to sympathetic blockade. Sympathetic blockade spreads two segments higher than the sensory blockade, which in turn spreads two segments higher than the motor blockade. Vasodilatation causes decrease in systemic vascular resistance and central venous pressure.[9-12] The same mechanism can sometimes lead to bradycardia. Main causes of bradycardia are shift in cardiac autonomic balance toward the parasympathetic system, activation of left ventricular mechanoreceptors from a sudden decrease in left ventricular volume (Bezold-Jarisch reflex) (BJR). It is suggested by pharmacological and animal studies that an important factor in initiating the BJR is 5-HT (serotonin) and blockade of 5-HT3 receptor can lead to attenuation of this reflex.[6]

It was shown by previous studies that Ondansetron 4 mg of Ondansetron administration has been occasionally used to decrease maternal hypotension and nausea.[9] Spinal anesthesia is the preferred anesthetic technique

for caesarean section as it is simple, safe, fast and reliable technique could effectively prevent maternal hypotension and nausea secondary to spinal anesthesia. Fetal morbidity increases by the decrease in cardiac output and uteroplacental flow caused by hypotension due to spinal anesthesia.[2] A very high sensory block requirement (till T5) in caesarean section causes extensive sympathetic blockade and hypotension in 55 to 90% of cases. Maneuvers like the partial left lateral decubitus (with the objective of limiting the aorto-caval compression caused by the gravid uterus) are partially effective. Vascular filling with crystalloids or starches and use of vasopressors are mainly used to treat hypotension but many studies showed these methods ineffective. It was shown by a recent review that hypotension is not prevented reliably by any one of these methods. To decrease fetal and maternal morbidity and mortality during spinal anaesthesia, it is crucial to prevent and treat it effectively. Ondansetron can be routinely used to prevent maternal hypotension and fetal compromise after spinal anesthesia in caesarean sections, as well as general surgical and other procedures performed in spinal anesthesia. It can be a good alternative for previously used methods to treat spinal induced hypotension. Ondansetron does not affect the heart and blood pressure, even when it is rapidly administered intravenously. In both children and adults, this drug is widely used to prevent postoperative nausea and vomiting prevention.

Based on above mentioned considerations, we conducted this randomized, controlled, double-blind study, that use of intravenous Ondansetron can be investigated and it can be used prophylactically for spinal induced hypotension. A total of 106 patients were enrolled in the study and were randomly divided into two equal groups. Hypotension occurred in 17.92% of patients in our study. The frequency of hypotension was significantly lower in the Ondansetron group (7.5%) as compared to placebo (28.3%). In a study conducted by Owczuk R et al,**Error! Bookmark not defined.** two equal groups were made out of 53 patients who operated under spinal anesthesia. It was observed that 48.1% patients in placebo group and 38.5% patients in onset group developed hypotension. They made the conclusion that Ondansetron is effective in preventing decrease in MAP and HR when compared to normal saline group. Their results were comparable to those observed in our study. In our study, we compared Ondansetron 6 mg with placebo. Owczuk et al. compared Ondansetron 8 mg with placebo. Sahoo et al. compared Ondansetron 4 mg with placebo.[5] Marashi et al. compared Ondansetron 6mg and 12mg with placebo.[3] Ortiz-Gómez et al.'s study [10] included three doses of Ondansetron (2, 4, and 8 mg versus placebo). Owczuk et al. and Marashi et al. studied a general surgical population. Sahoo et al. and Ortiz-Gómez et al used obstetric patients in their study. We on the other hand, studied patients undergoing urological, orthopedic and gynecological surgeries.

Anesthetic technique and dose is a very important factor that can cause the difference between the studies. A different dose of hyperbaric bupivacaine was used in all of these above-mentioned studies. We and Marashi et al. used 15mg of hyperbaric bupivacaine for spinal anesthesia. Sahoo et al. used 10 mg bupivacaine, Owczuk et al used 20 mg bupivacaine. Ortiz-Gómez et al. personalized each dose to each patient (9.7 ± 0.4 mg in the placebo group and 9.6 ± 0.3 mg in Ondansetron group), and the mean dose was smaller than our dose of 15mg. This was a good method as it can be used to prevent over or under dosing of patients. Another difference is that intravenous fentanyl to treat pain and tramadol or promethazine to treat adverse effects was used by Sahoo et al. Blood pressure readings can be modified directly or indirectly by these medications due to a central mechanism. Another difference is that we do not use intrathecal opioids for improving effect of spinal anesthesia. This is different from the study of Ortiz-Gómez et al. in which intrathecal fentanyl was used. Ondansetron may be centrally acting and its mechanism can be affected by intrathecal opioids. Neither we nor Ortiz-Gómez et al used other supplemental analgesia, and patients who required it were not included in the study. Earlier studies have suggested that when Ondansetron is administered intravenously, it can antagonize sensory block produced by local anesthetics given intrathecally. This is perhaps the reason for the attenuated hemodynamic responses after spinal anesthesia.

To summarize, in the current study, we investigated the effects of 6 mg of Ondansetron on the patients' MAP. We

observed that 6 mg of Ondansetron intravenous, when given alongside rapid crystalloid infusion, could significantly reduce the incidence of spinal induced hypotension. However, Ondansetron preloading did not appear to have any significant effect in reducing hypotension in gynecologic and orthopedic surgeries. We can assume that 6 mg of Ondansetron may not be sufficient to prevent hypotension in these types of surgeries. It seems that Ondansetron enhances the contractility and efficiency of the heart by acting at cardiac level and stabilizes systemic vascular resistance by acting at vascular level through vascular and/or medullary specific receptors.

Conclusion

Ondansetron is effective in preventing hypotension in patients undergoing spinal anesthesia.

Recommendations

We do feel the need to include other important variables like heart rate, systolic and diastolic blood pressures. The duration and type of surgery, blood loss and maintenance fluid requirements can influence results of such studies. Further studies should be carried out, taking into consideration these aspects too. Studies should also be done that involve more invasive hemodynamic monitoring like Swan-Glanz catheter. It can be helpful to properly assess decrease in venous return and cardiac filling pressures. The effect of different doses of Ondansetron on reducing spinal induced hypotension also needs to be further investigated.

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