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Preventing Hypotension in Patients Undergoing Spinal Anaesthesia: The Role of Propylactic Ondansetron in Obstetric and Non-Obstetric Patients

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ABSTRACT

Background and Aims: Many surgical operations may be safely and effectively performed using spinal anesthesia (SA). The activation of 5-HT3 receptors in vagal nerve terminals is known to cause hypotension, bradycardia, and vasodilation, which are symptoms of the Bezold Zarisch reflex, which is associated to SA1,2. The 5-HT3 receptor blocker ondansetrona, when used prophylactically, may mitigate the adverse effects.This research aims to test the concept that SA-induced hypotension and bradycardia may be mitigated by blocking type 3 serotonin receptors with intravenous ondansetron.

Method: One hundred forty individuals who were about to get SA were the ones studied. Two groups of people were analyzed: those who were pregnant and those who were not. A separate control group was established for each demographic grouping. Transporting the patient to the operating room allowed for the establishment of venous access and the connection of basic monitors. There was a baseline assessment of the patient's vitals taken before to the SA. Afterwards, SA was administered while the patient was seated. Following spinal drug delivery, vital signs such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and oxygen saturation (Sp02) were monitored continuously for 18 minutes, with 2-minute intervals in between. We kept an eye out for side effects like vomiting and nausea. Intravenous ephedrine 6 mg was used to treat a decrease in systolic blood pressure to 90 mm Hg or lower, while intravenous glycopyrrolate 0.2 mg was used to treat a reduction in heart rate to fewer than 50 beats per minute. Also recorded were the dosages of ephedrine and glycopyrrolate.The groups were compared using Student's t-test for normally distributed continuous variables. Depending on the situation, we used either the Chi-square test or Fisher's exact test to compare the groups' nominal categorical data. A p-value less than 0.05 was deemed to have statistical significance.

Result: The obstetric group had a 44.3% incidence of hypotension. Hypotension affected 54.3% of patients in the placebo group (n=19), compared to 34.3% of patients in the study group (n=12). Out of all the people surveyed, 7.1% had hypotension who were not pregnant. The control group had a rate of 14.3%. The number of patients receiving ephedrine did not change significantly across groups (p= 0.092). In group A1, the average amount of ephedrine consumed up to delivery time was 12 mg, whereas in group A2, it was 21.79 mg. A rate of 2.9% was seen for bradycardia in the obstetric group. This occurrence was unique to group A1.In group A1, the HR decreased from an average pre-operative value of 99.4±16.84 to a minimum of 88.57±21.57 in only 8 minutes, whereas in group A2, it decreased from an average pre-operative value of 94.57±17.96 to a minimum of 82.23±17.78. A rate of 2.9% was found in group B1, whereas 5.7% was found in group B2. In group B1, the heart rate

decreased from 83.17±19.67 to 74.34±17.62 in only 18 minutes, according to the trend of heart rate comparisons. With the first half an hour following surgery, group B2's heart rate dropped from an average of 87.54±13.53 to a low of 69.91±11.81.

Conclusion: Both the obstetric and non-obstetric populations saw a small but statistically significant decrease in the occurrence of hypotension when ondansetron was administered prophylactically, according to our research. Patients who were pretreated with ondansetron used a much lower dosage of vasopressor for hypotension, however the number of patients who needed vasopressor for therapy did not decrease with 5-HT3 antagonist. Therefore, it may be possible to prevent adverse fetal consequences caused by the excessive use of vasopressors by pretreating with Ondansetron.

1. INTRODUCTION

A skilled anesthetist has mastered the art of administering anesthesia in a way that ensures a safe and successful procedure with minimum adverse effects and a speedy recovery.
For many surgical procedures, spinal anesthesia is a viable alternative to general anesthesia because it efficiently provides intraoperative analgesia by the injection of a local anesthetic medication into the cerebrospinal fluid. For elective cesarean sections, it has replaced other anesthetic techniques due to its simplicity, speed, reliability, and safety.
There is a high incidence of hemodynamic instability with this technique, despite its widespread usage and relative simplicity of use. Hypotension and bradycardia are the most common of these, with an estimated 33% and 13% occurrences in the general population, respectively, outside of the obstetric setting.One, two Hypotension occurs in an estimated 50-60% of pregnant women who are not in labor.Fetal hypoxia, acidosis, and brain damage may occur as a result of placental hypoperfusion, as well as pulmonary aspiration, vomiting, and nausea in the mother. 1,2 In extreme circumstances, hypotension can cause the mother to lose consciousness.3 Consequently, prompt and efficient prevention and treatment are of the utmost importance.

The FDA has authorized the use of the selective 5-HT3 receptor antagonist ondansetron to alleviate vomiting and nausea brought on by radiation, chemotherapy, and surgery. 7 .Ondansetron is classified as a pregnancy category B drug by the FDA since it has not been shown to affect the offspring of animals studied in these trials. A small trial included 176 pregnant women found no evidence that ondansetron increased the incidence of significant abnormalities above baseline 8. Despite their being a

The use of ondansetron to alleviate nausea and vomiting during pregnancy has been supported by human evidence, and there have been no reports of damage to either the mother or the unborn child from this medication.
This research set out to test the idea that spinal anesthesia-induced hypotension and bradycardia may be mitigated by reducing type 3 serotonin receptor blockage with intravenous ondansetron. Also investigated were ondansetron's effects on nausea, vomiting, and the usage of vasopressors.

2. METHODS

The present study was carried out at the Department of Anesthesia, Indraprastha Apollo Hospital. New Delhi for 2 years from 2016 to 2018. After obtaining due institutional approval and informed written consent from 140 patients of American society of Anesthesiologist (ASA) physical status Grade 1 and 2.

Study type: Prospective, interventional, randomized, controlled, double blinded study.

Study design: Allocation- Randomised

End point of study- 18 minutes

Interventional Model- Parallel Assignment

Masking- Double Blinded; (Subject, Caregiver, Outcome Asessor are not involved in the study).

The study was done on 2 sets of population undergoing spinal anesthesia. Each group consisting of 35 patients

Group A: Obstetric patients undergoing LSCS.

A1: Received ondansetron (dose-100 mcg/kg BW) diluted in 10 ml of NS iv 5 min before SA **A2:** Received 10 ml NS iv 5 min before SA

Group B: Non obstetric patients undergoing orthopaedic, urological, gynecological procedures under SA

B1: Received ondansetron (dose- 100 mcg/kg BW) diluted in 10 ml NS iv 5 min before SA **B2:** Received 10 ml NS. Iv 5 minutes before SA

Study population

- **Inclusion criteria-** Patients with following criteria were included

1. Adults above 20 years
2. ASA 1 to ASA 2 status
3. Height- more than 150cm
4. BMI 20 to 35 kg/m^2

- **Exclusion Criteria-** Patients with following feature were excluded

1. Those refusing for participation
2. Patients with uncontrolled arterial hypertension, coronary heart disease.
3. Contraindications of subarachnoid block like
    a. Raised intracranial pressure
    b. Known history of coagulation disorders

c. Inflammatory skin lesions at lumbar region
d. Hypovolemia
e. Marked spinal deformity

4. Allergy to local anaesthetics
5. Sinus Bradycardia (Heart rate <60 beats/min.); Second or third degree heart block.
6. Patients receiving selective serotonin reuptake inhibitors or migraine medications. 7. Age below 20 years

PREOPERATIVE PREPARATION:

On the night before surgery:
Preoperative evaluation of all the patients was done which incuded detailed history and clinical examination and lab investigations which included blood grouping and haemoglobin. All the patients were allowed to take light diet in the evening of previous day of operation and were advised to remain nil per oral after midnight.

PROCEDURE: Following transfer to the operating room, the patient had venous access insertion and the placement of several monitors, including non-invasive blood pressure, electrocardiography, and pulse oximetry, which measure oxygen saturation. Before spinal anesthesia, the patient's vitals were recorded, including blood pressure and heart rate.
We used 6 milliliters of Ringer Lactate per kilogram of body weight for coloading.
It was not the same anesthesiologist who administered the medicine and monitored the patient; it was someone else entirely who made the study solution.

After 2cc of 2% Lignocaine infiltration with a 27G whitacre needle, spinal anesthesia was administered at the L3-L4 or L2-L3 level to obstetric patients in Group A (10 mg) and patients in Group B (15 mg) under strict aseptic conditions.
Patients were promptly put in the supine posture after spinal procedures, and all obstetric patients had a prefabricated wedge of 15 degrees inserted under their right flank. When the infant was retrieved and the umbilical chord clamped, the oxygen was administered via the Hudson mask at a rate of 6 liters per minute, regardless of the patient's oxygen saturation. Using the feeling loss to cold swab test, we were able to identify the upper and lower degrees of sensory block.
At the moment of spinal drug delivery and at 2-minute intervals up to 18 minutes later, the following vital signs were recorded: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and oxygen saturation (Sp02).
We kept an eye out for side effects like vomiting and nausea. The patient was given 6 mg of ephedrine intravenously to bring the systolic blood pressure down to 90 mm Hg or lower, and 0.2 mg of glycopyrrolate intravenously to bring the heart rate down to 50 beats per minute or lower.

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3. RESULTS

All parameters were compared within the two groups to find if there was a protective effect of ondansetron on prevention of hypotension following spinal anesthesia and if the response was different in the two different population of patients (Obstetric and non obstetric). Data obtained are presented as mean ± SD and as count (%). Two sided p values of <0.05 were considered significant

Hypotension - Hypotension was defined as SBP less than 90 mmHg. We also considered SBP less than 90 mmHg as a threshold for treatment of hypotension; this was standardized to boluses of ephedrine 6 mg given incrementally until SBP was more than 90 mmHg.
Incidence of hypotension in obstetric group was found to be 44.3% . Percentage of patients having hypotension in placebo group was 54.3% (n= 19) and in study group 34.3% (n=12). Although more number of patients in control (placebo) group has hypotension these differences were not statistically significant (p= 0.092).

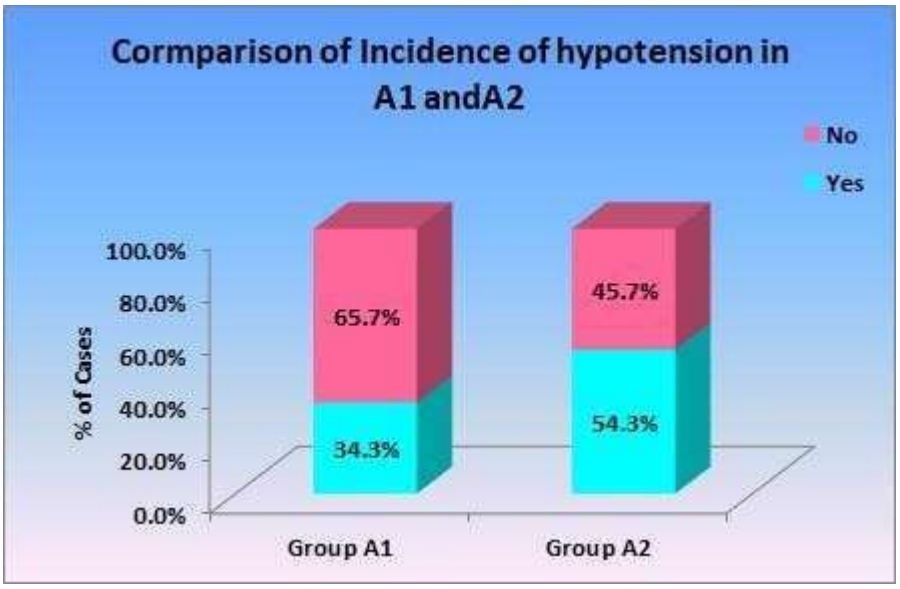

Figure 1: Bar diagrams of incidence of Hypotension observed in the group A1 and A2

On comparing SBP trend among obstetric group, drop in SBP was found in both the study and control groups after SAB. SBP dropped from mean preop value of 131.83±16.51 to minimum value of 114.4±19.44 at 14 minutes in group A1. In group A2 it dropped from mean preop value of 131.06±13.57 to minimum of 110.6±28.5 in 12 min.
Although the fall in SBP was more in control group A2, The difference in fall of SBP was not statistically significant between the groups after SAB.

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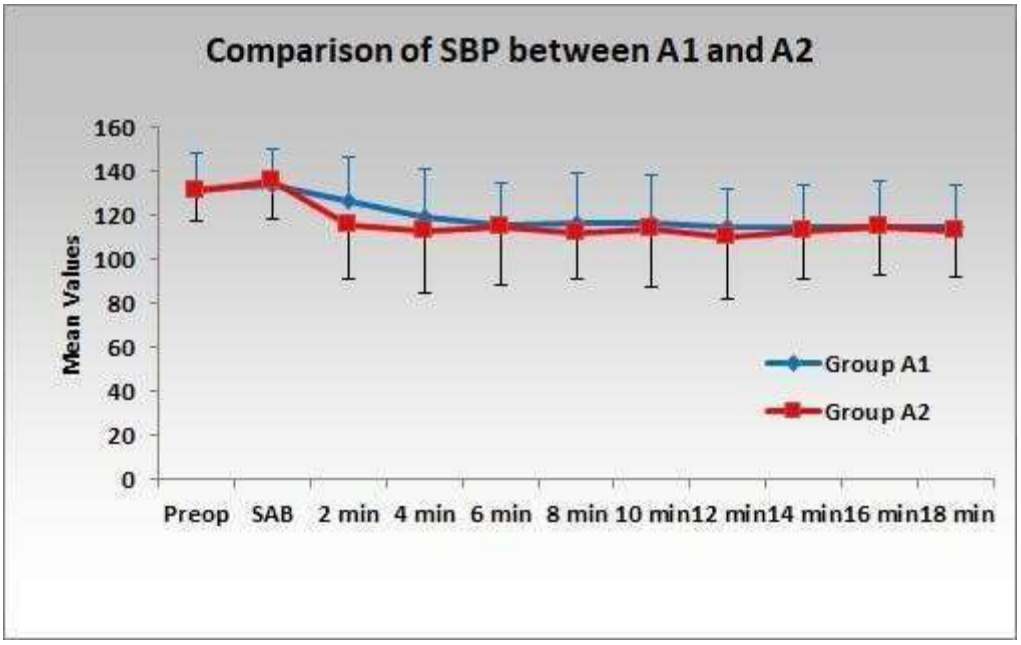

Figure 2: Comparing SBP variation between A1 and A2. Shows SBP variation between the two groups from preoperative value to 18 min after SAB. Although there was drop in SBP in both the groups and comparatively drop was more in group A2 after SAB but the difference was not statistically significant.

On comparing the DBP trend in group A1 and A2, in group A1 DBP dropped from mean preop value of 81.8±13.38 to minimum of 62.66±15.71 in 12 min and in group A2 from mean preop value of
79.00±12.00 to minimum of 58.20±9.80 in 14 min.
The difference in drop of DBP between two groups was statistically significant only at 14 min p value 0.030

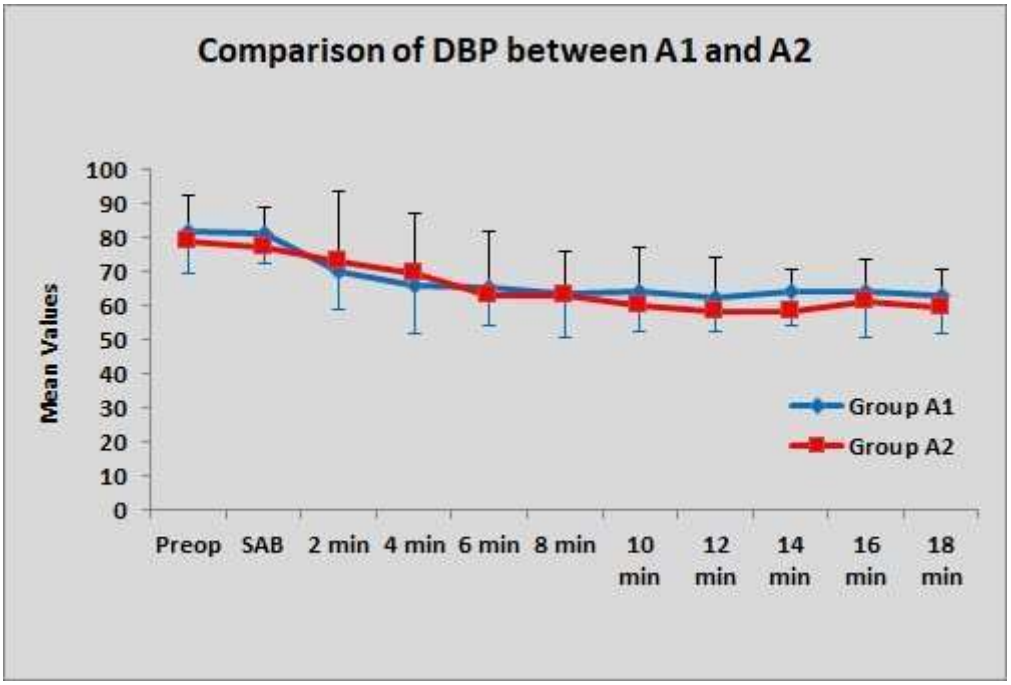

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Figure 3: Comparison of DBP variations between groups A1 and A2. Shows DBP variation between the two groups from preoperative value to 18 min after SAB. There was drop in DBP in both the groups but more in group A2 and it was also statistically significant at 14 minutes

On comparing MAP trend in obstetric population, in group A1 MAP dropped from preoperative mean value of 97.74±11.36 to minimum value of 78.77±12.17. In group A2 MAP dropped from preoperative mean value 97.46±12.62 to minimum value of 76.89±19.12 in 12 min.
The drop in mean blood pressure was similar in both groups.

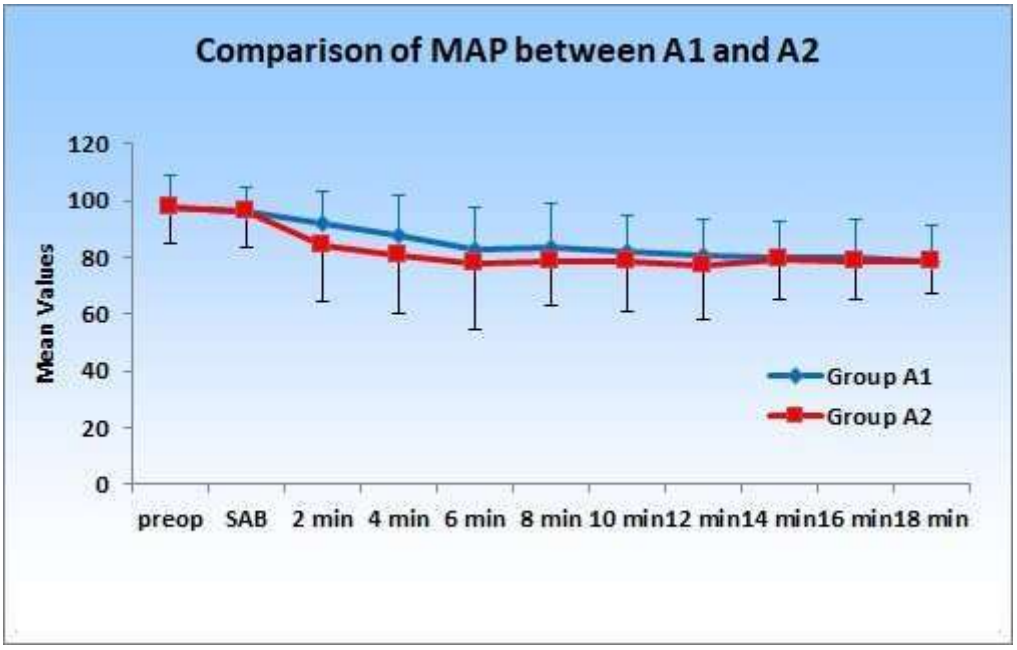

Figure 4: Comparison of MAP variations between groups A1 andA2

Overall Incidence of hypotension in non obstetric population in present study was found to be 7.1% .
Incidence in control group was 14.3%. The difference was not significant.
On comparing SBP trend in group B, SBP in group B1 dropped from preop mean value of 144.57±14.09 to minimum of 126.17±15.48 in 12 min. In group B2 it dropped from preop mean value of 146.69±17.41 to minimum of 123.03±24.18 in 12 min.
The difference in fall of SBP was not statistically significant between the groups.

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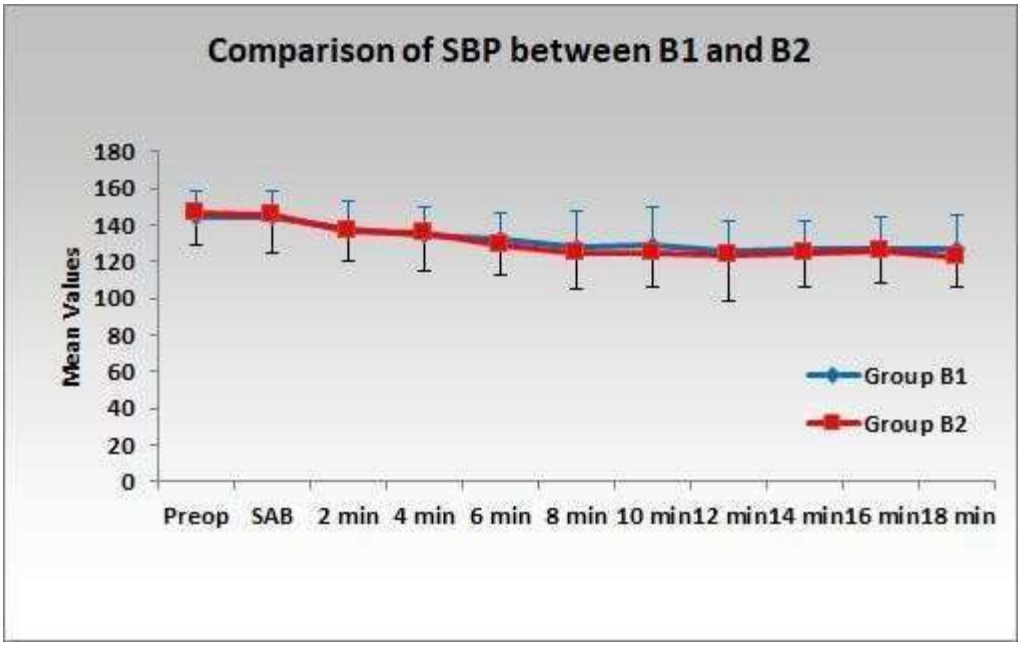

Figure 5: Comparison of SBP variation in B1 and B2. Diagram showing SBP variation between the two groups from preoperative value to 18 minutes after SAB. There was no significant difference between the two groups

On comparing DBP trend in non obstetric population, in group B1, DBP dropped from mean preop value of 80.57±16.66 to minimum of 71.49±12.74 at 14 min. In group B2 DBP dropped from mean preop value of 84.31±11.13 to 68.63±11.84 in 14 min.
The difference in drop between two groups was not statistically significant.

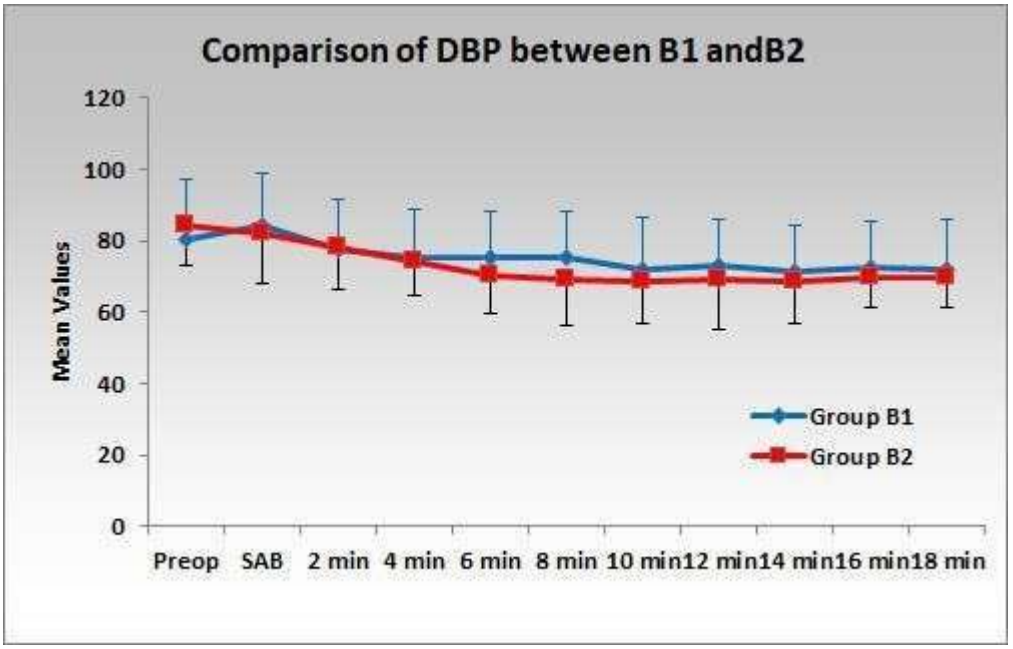

Figure 6: Comparison of DBP variation in B1 and B2. Diagram showing DBP variation between the two groups in non obstetric population. There was fall in DBP in both the groups but the difference was not statistically significant

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On comparing MAP trend in non obstetric population, in group B1 the MAP dropped from preop mean value of 95.83±14.83 to minimum of 84.6±12.27 in 14 min whereas in group B2 it dropped from mean preop value of 97.09±11.46 to minimum of 79.37±17.5 in 8 min.
There was statistically significant difference in fall of MAP between the two groups at 6 min and 8 min p values of 0.027 and 0.031 respectively.

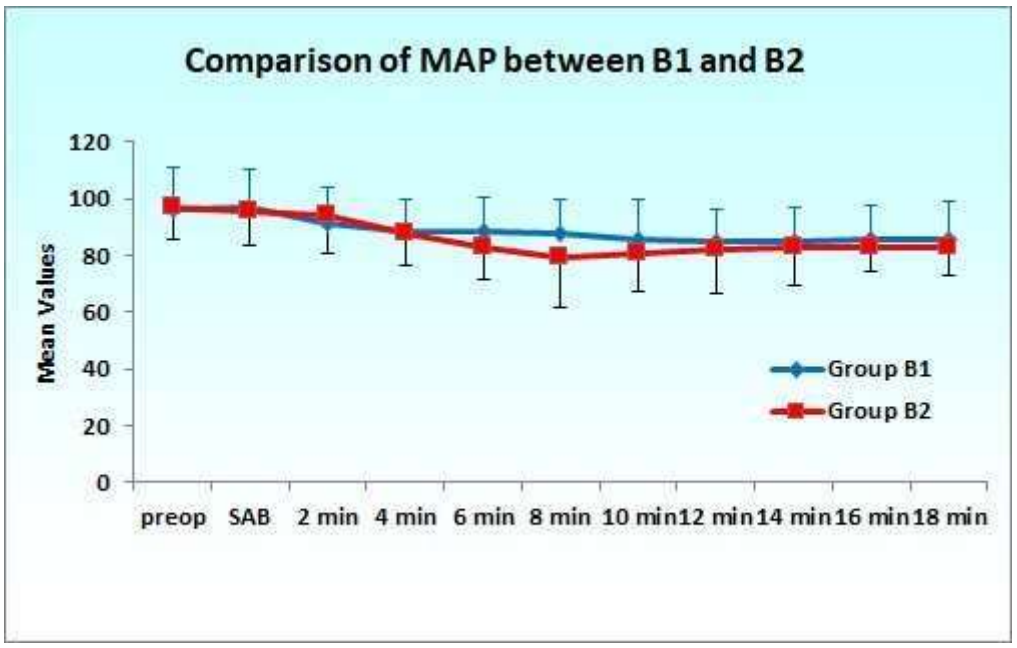

Figure 7: Comparison of MAP variations between B1 and B2 . Diagram showing of fall in MAP in both groups of non obstetric population after SAB. The drop is more in group B2 which is statistically significant with p values= 0.027 and 0.031 at 6 min and 8 min

EPHEDRINE CONSUMPTION- We found no significant differences between groups in the number of patients requiring ephedrine (p= 0.092). However there was a significant difference in total consumption of ephedrine between group A1 and A2 (p= 0.007). The mean consumption of ephedrine upto delivery time was 12 mg in group A1 and 21.79 mg in group A2, suggesting that prophylactic ondansetron administration significantly reduced the severity of hypotension and hence the required dose of ephedrine.

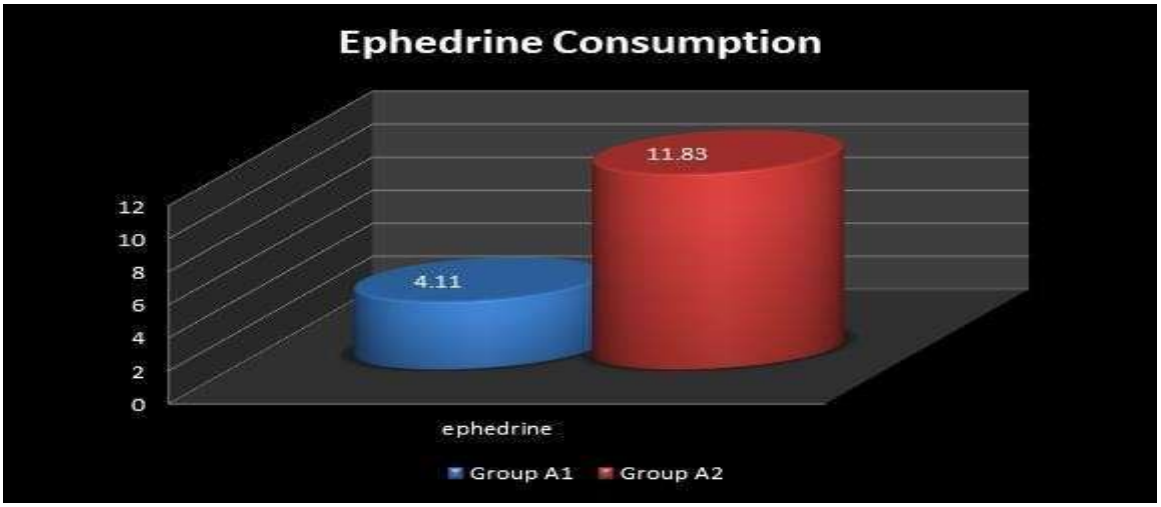

Figure 8: Bar diagrams showing the amount ephedrine consumption in groups A1 and A2

Shows increased requirement of ephedrine in control group among obstetric population which is statistically significant with p value of 0.007. Since its a quantitative data paired t test was applied

Among the non obstetric population since hypotension was seen only in group B2 so ephedrine requirement was seen only in this group. .

BRADYCARDIA - Bradycardia was defined as heart rate less than 50 beats/ min and was treated with intravenous ephedrine if bradycardia was accompanied with hypotension and glycopyrrolate if only bradycardia was there without hypotension. Incidence of bradycardia in obstetric group observed was 2.9%. The event was found only in group A1. As mentioned already, bradycardia connected with spinal blockade occurs at a rate almost 3 times less than hypotension, so in an observed group of patients, frequency of the event was too small to observe significant differences

On comparing the trend of heart rate in obstetric population, in group A1 the HR dropped from mean preop value of 99.4±16.84 to lowest value of 88.57±21.57 whereas in group A2 it dropped from mean preop value of 94.57±17.96 to lowest value of 82.23±17.78 in 8 min. there was statistical significant difference at 6 min and 8 min with p value 0.019 and 0.007 respectively. Hence ondansetron significantly reduced drop in heart rate

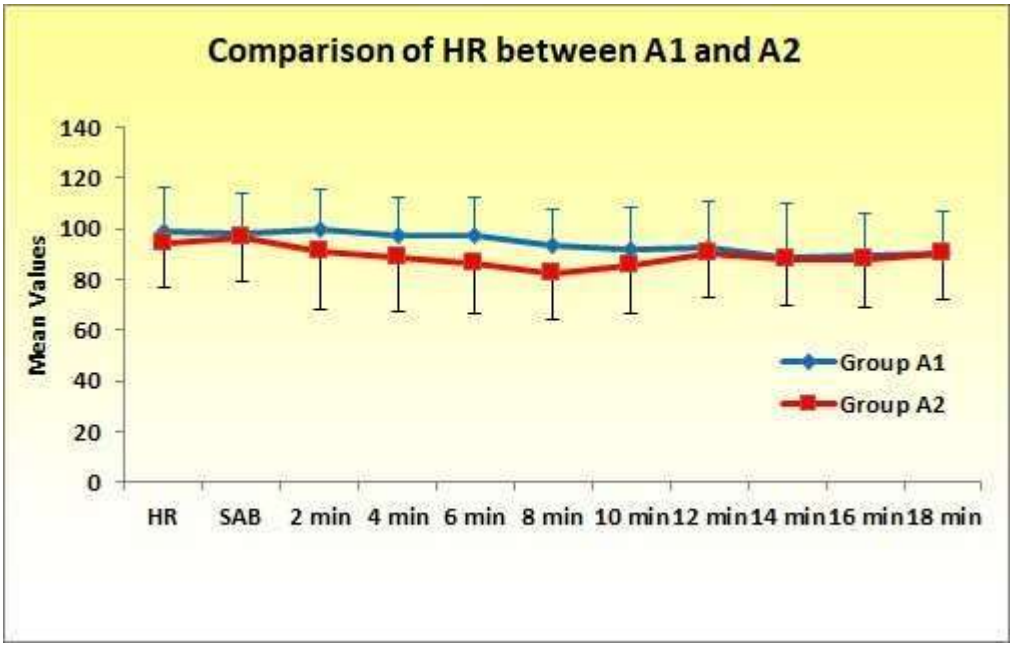

Figure 9: Comparison Heart Rate variation between A1 and A2. Diagram showing Heart Rate variation between the two groups of obstetric population. There is significant drop in HR in group A2 at 2 minutes and 6 minutes

Incidence of bradycardia in non obstetric population was found to be 4.2%. In group B1 incidence was 2.9% and in group B2 it was 5.7%. although the incidence was more in group B2, difference was not statistically significant.
On comparing the trend of heart rate, in group B1 there was fall in HR from mean preop value of

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83.17±19.67 to lowest of 74.34±17.62 in 18 min. In group B2 the HR fell from mean preop value of 87.54±13.53 to lowest of 69.91±11.81 in 18 min. More drop was seen in group B2 but it was not statistically significant when compared with group B2. There was a definite tendency towards lower incidence of bradycardia in patients pretreated with ondansetron.

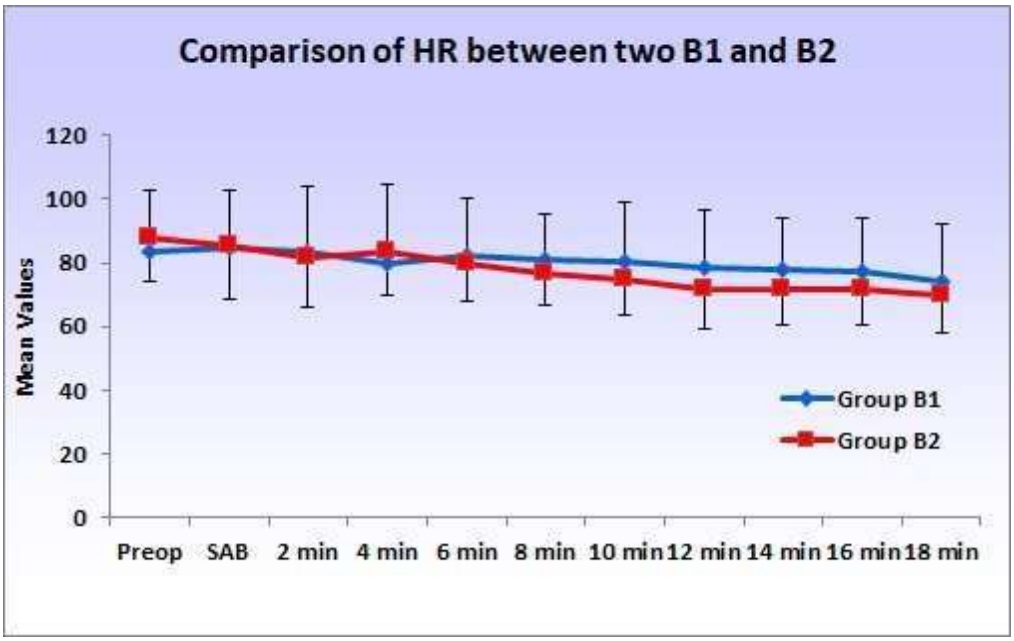

Figure 10: Heart Rate variation between B1 and B2

VOMITING -Nausea and vomiting under spinal anesthesia is usually following a drop in blood pressure and probably as consequence of cerebral hypoxia. Ondansetron appears to protect against this. None of the patients in obstetric or non obstetric population pretreated with ondansetron had vomiting. However since the overall incidence of vomiting was low (2.8%). the difference was not significant.

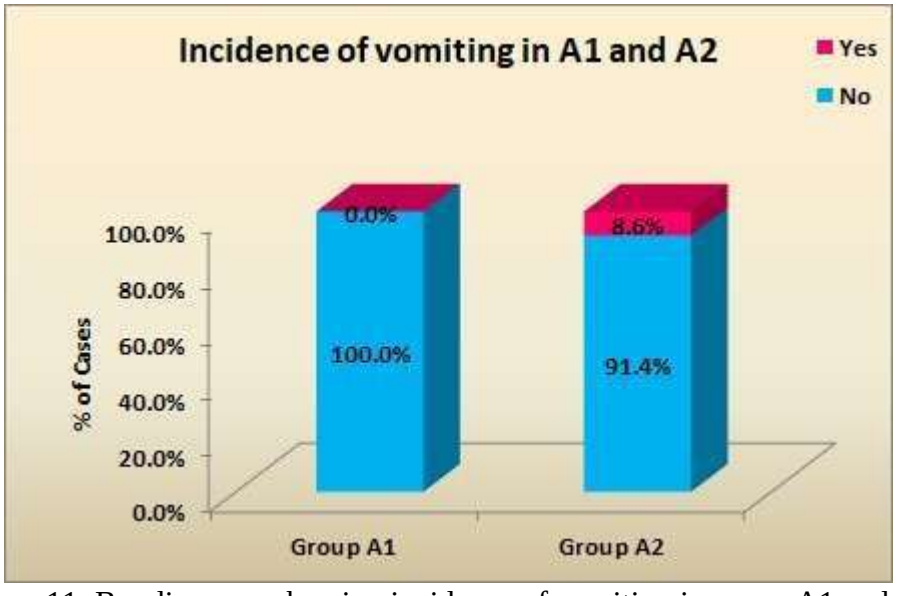

Figure 11: Bar diagrams showing incidence of vomiting in group A1 and A2

Incidence of vomiting seen in obstetric population is 8.6%. It is seen only among control group. There is no significant difference. Between the group

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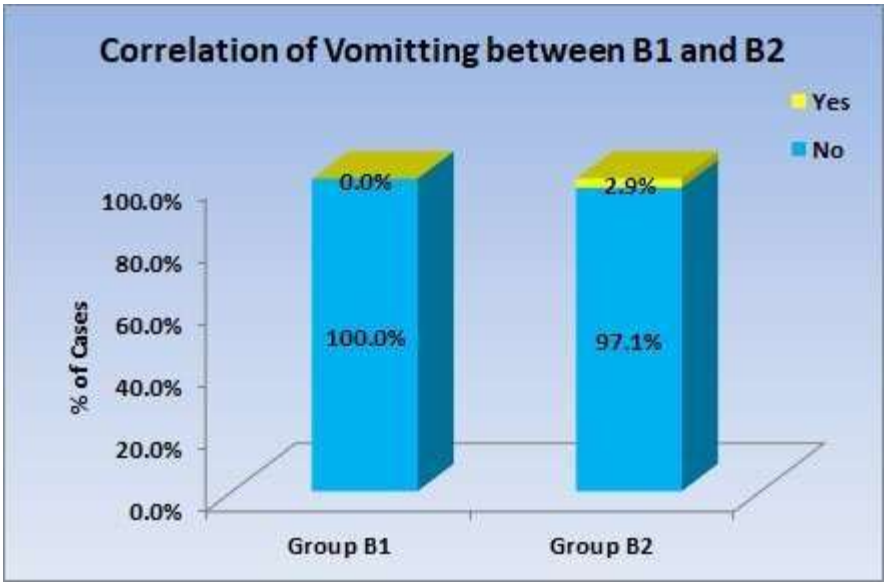

Figure 12: Bar Diagrams showing incidence of vomiting in groups B1 and B2
The incidence of vomiting was very low overall and was seen only in control group

4. DISCUSSION

Spinal anesthesia is a safe and effective anesthetic for a range of surgical procedures especially for caesarean section, considering its simplicity, rapidity of action , dense neural block, analgesia and minimal fetal exposure to drugs[4]. . Hemodynamic changes are usually benign; however , in selected cases, they may lead to serious consequences , including cardiac arrest. Cardiac arrest is a consequence of progressive bradycardia rather than progressive hypotension [5,6] . This complication results from hyperactivity of the vagal nerve.[5]
It is worth emphasizing that the mechanisms responsible for blood pressure drop may be different from those producing severe bradycardia and cardiac arrest. Hypotension is due to a decrease in systemic vascular resistance and central venous pressure, which originates from sympathetic block, and blood redistribution in lower limbs. Bradycardia on the other hand is a consequence of Bezold-Jarisch reflex and an increase in baroreflex activity.
Methods of decreasing the extent of cardiovascular consequences of spinal anesthesia include preloading with intravenous fluid infusion, administration of vasoconstricting agents, placing patients in positions facilitating venous return and administration of atropine.[3, 5]
Spinal anesthesia- related triggering of Bezold-Jarisch reflex, demonstrated by hypotension, bradycardia and vasodilatation, is known to result from stimulation of 5-HT_3 receptors in vagal nerve endings [9,10]. Hence the idea of using ondansetron,a 5 HT3 antagonist to block this reflex.
In 2004, Martinek described the case of circulatory cessation in asystole during spinal anesthesia, which was successfully treated with intravenous ondansetron and atropine.[9]
Animal studie have demonstrated that 5 HT_3 receptor blockade decreases the intensity of signs related to BJR triggered by various factors.[11, 12]
Ondansetron was shown to attenuate arterial blood pressure drop due to spinal anesthesia in general surgery population in a study by Owczuk et al[13] and in obstetrical population in a

study by Sahoo et al.[14]. However, it was not shown to decrease this risk in obstetrical population in study of Oritz-Gomez et al[16] and in obstetrical population by Trabelsi et al[15].

In current study we investigated the effects of ondansetron pretreatment on prevention of hypotension in two sets of population obstetric and non obstetric along with their controls.

Owczuk et al[13] compared ondansetron 8 mg (n= 35) with placebo (n= 36), and Sahoo et al[14] compared ondansetron 4mg (n=24) with placebo (n= 24) while Oritz Gomez et al[16] study included three doses of ondansetron (2,4 and 8 mg versus placebo). Our study compared ondansetron at dose of 0.1mg/kg BW (n = 35) with placebo (n= 35).

For Obstetric patients we did not extend data analysis beyond delivery time for hemodynamic variables. Therefore we excluded factors that might affect blood pressure after delivery such as oxytocin use, blood loss and pelvic exenteration. We kept the same time interval for non obstetric cases also.

One of the causes of hypotension and bradycardia associated with spinal anesthesia has been attributed to BJR. A rationale for the use of 5- HT3 antagonist is based on fact that 5-HT3 agonist like veratridine activates the reflex. Although animal studies have been suggestive of blocking the BJR by 5-HT3 antagonists but whether these receptors actually participate in any reflex in human beings has been questioned by few authors.

So although we did not find a significant reduction in the incidence of hypotension after ondansetron, it was obvious by the results that the severity of hypotension was much less in the ondansetron pretreated group. The amount of ephedrine used was significantly more in the control group. Since BJR is activated during hypovolemia, it would have been interesting to see the difference in incidence of hypotension and bradycardia in patients who bled, especially in the obstetric population. We terminated the readings before the delivery of baby so as not to have confounding factors.

Nausea and vomiting under spinal anesthesia is usually following a drop in blood pressure and probably as consequence of cerebral hypoxia. Ondansetron appears to protect against this. None of the patients in obstetric or non obstetric population pretreated with ondansetron had vomiting. However since the overall incidence of vomiting was low (2.8%). the difference was not significant.

LIMITATIONS

We acknowledge several limitations in our study:-

1. We could not compare the obstetric group with the non obstetric group because the two populations were incomparable in terms of gender and age.
2. Definition of hypotension was different in few studies which we took for comparison. Oweczuk did not supply a definition of hypotension while Sahoo used a SBP < 90 mmHg or DBP < 60 mmHg. Our definition of hypotension was similar to Oritz-Gomez and Trabelsi study. The definition of hypotension affects the incidence.
3. We terminated the study before the administration of oxytocin and delivery of the baby so as not to have confounding factors. Hence, we could not assess the effect of ondansetron in the presence of blood loss and hypovolemia.
4. Fixed dose of Bupivacaine was used irrespective of height and weight. That could have affected our results.

5. Though there was no significant difference in age, body weight, height, ASA status. Sex distribution was significant in study group of non obstetric population and it may suggest a potential impact on study results. Analysis performed by Hartman et al did not prove that relevant hypotension due to SA has significant connections with patients gender. This point diminishes the risk of mentioned bias.

6. CONCLUSION

1. It was discovered in our research that the incidence of hypotension was marginally reduced in both the obstetric and non-obstetric populations when ondansetron, a 5HT-3 receptor antagonist, was administered prophylactically.
2. While the number of patients requiring vasopressor for hypotension therapy was not reduced by 5-HT3 antagonist, individuals pretreatment with ondansetron utilized a much lower dosage of vasopressor. Pretreatment with ondansetron may reduce the risk of adverse effects on the developing baby.
3. There was no vomiting reported by any of the research groups. In general, only 2.9% of patients had vomiting.

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