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Original Research Article

EFFICACY OF PROPHYLACTIC ONDANSETRON ON PREVENTION OF HYPOTENSION INDUCED BY SPINAL ANESTHESIA IN OBSTETRIC AND NON OBSTETRIC PATIENTS

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ABSTRACT

Background and Aims: Spinal anesthesia (SA) is safe and effective technique for a range of surgical procedures. SA related triggering of Bezold Zarisch reflex demonstrated by hypotension, bradycardia and vasodilation is known to result from stimulation of 5-HT3 receptors in vagal nerve endings[1,2,]. Prophylactic administration of ondansetrona a 5-HT_3 receptor blocker may reduce the side effects.

The aim of the present study is to verify the hypothesis that blockage of type 3 serotonin receptors by intra venous ondansetron administration would reduce hypotension and bradycardia induced by SA.

Method: The study was conducted on 140 patients undergoing SA . There were two sets of population, obstetric and non obstetric. Each set of population had their own control group. After taking the patient to the operation theatre, venous access was established, and basic monitors were connected . Base line blood pressure and heart rate were noted before the SA.. Then in sitting position, SA was performed . After spinal, Heart rate(HR), systolic(SBP), diastolic (DBP) and mean arterial pressure (MAP), and oxygen saturation ($Sp0_2$) were recorded at time of spinal drug administration and at 2 min intervals upto 18 min. Adverse effect such as nausea and vomiting, were monitored. Drop in systolic blood pressure to less than or equal to 90 mm of Hg was treated with iv ephedrine 6 mg and HR fall to less than 50 beats per minute with iv 0.2 mg glycopyrrolate . Amount of ephedrine and glycopyrrolate consumed were also noted.

The comparison of normally distributed continuous variables between the groups was performed using Student's t-test. Nominal categorical data between the groups were compared using Chi- squared test or Fisher's exact test as appropriate. $P< 0.05$ was considered statistically significant..

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Result: 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). Overall Incidence of hypotension in non obstetric population was found to be 7.1% . Incidence in control group was 14.3%. No significant differences between groups in the number of patients requiring ephedrine (p= 0.092).). The mean consumption of ephedrine upto delivery time was 12 mg in group A1 and 21.79 mg in group A2 . Incidence of bradycardia in obstetric group observed was 2.9%. The event was found only in group A1.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 . In group B1 incidence was 2.9% and in group B2 it was 5.7 On comparing the trend of heart rate, in group B1 there was fall in HR from mean preop value of 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

Conclusion: Our study found that prophylactic administration of ondansetron produced an insignificant reduction in the incidence of hypotension in both, obstetric and non obstetric population. 5-HT_3 antagonist did not lower the number of patients who required vasopressor for the treatment of hypotension, but the dose of vasopressor used was significantly lower in ondansetron pretreated patients. Hence Ondansetron pretreatment has the potential to avoid harmful fetal effects secondary to excessive use of vasopressors.

1. INTRODUCTION

Delivery of safe and effective anesthesia with minimal side effects and rapid recovery is an art attributed to a good anesthetist.

Spinal anesthesia, whereby a local anesthetic drug is injected into the cerebrospinal fluid, is an efficient method of providing intraoperative analgesia and alternative to general anesthesia for many surgical procedures. Since it is simple, fast to perform, reliable and safe, it has become the anesthetic technique of choice for elective caesarean section.

Despite the popularity and ease of its use, this procedure is frequently associated with hemodynamic instability. In most cases , these include hypotension and bradycardia, the incidence of which is estimated to be 33% and 13% , respectively in the non obstetric population.[1,2] In obstetric, non labouring patient, the incidence of hypotension has been estimated to be as high as 50%-60%.[1,2] Hypotension may be associated with maternal nausea and vomiting and in severe cases unconsciousness, pulmonary aspiration and placental hypoperfusion leading to fetal hypoxia, acidosis and neurologic injury.[3] It is therefore crucial to prevent and / or treat it quickly and effectively.

Ondansetron is a selective 5-HT_3 receptor antagonist and is currently approved by the Food and Drug Administration (FDA) for treatment of nausea and vomiting caused by chemotherapy, radiation therapy and surgery [7] .The FDA has assigned ondansetron to pregnancy category B, animal studies demonstrate no harm to their offspring. A limited study was conducted in 176 pregnant females which showed that ondansetron does not appear to be associated with an increased risk for major malformations above baseline [8] . Although limited

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human data exists, ondansetron is frequently given to parturient patients to help prevent nausea and vomiting without any reported maternal or fetal harm.
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 spinal anesthesia. In addition, the effects of ondansetron on vasopressor consumption and the incidence of nausea and vomiting were also studied.

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

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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: After taking the patient to the operation theatre, venous access was established, monitors were connected which included non invasive blood pressure, electrocardiograghy and oxygen saturation through pulse oximetry. Base line blood pressure and heart rate were noted before the spinal anaesthesia.

Coloading was done with 6ml/kg BW of Ringer Lactate .

The anaesthesiologist who prepared the study solution was different from, the one who injected the drug and observed the patient.

Then under all aseptic precautions with patient in a comfortable sitting position, spinal anesthesia was performed at L3-L4 or L2-L3 level (after 2cc of 2% Lignocaine infiltration) with a 27G whitacre needle, using 0.5% hyperbaric Bupivacaine in a dose of 10mg for the obstetric patients in group A and 15 mg in Group B patients.

After spinal, patients were immediately placed in supine position and a preformed wedge of 15 degrees was kept under the right flank for all obstetric patients Oxygen was given through the hudsons mask at the rate of 6 liter per minute irrespective of oxygen saturation till the baby was extracted and umbilical cord clamped. The upper and lower levels of sensory block was determined using loss of sensation to cold swab .

Heart rate(HR), systolic(SBP), diastolic (DBP) and mean arterial pressure (MAP), and oxygen saturation ($Sp0_2$) were recorded at time of spinal drug administration and at 2 min intervals upto 18 min.

Adverse effect such as nausea and vomiting, were monitored. Drop in systolic blood pressure to less than or equal to 90 mm of Hg was treated with iv ephedrine 6 mg and HR fall to less than 50 beats per minute with iv 0.2 mg glycopyrrolate.

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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).

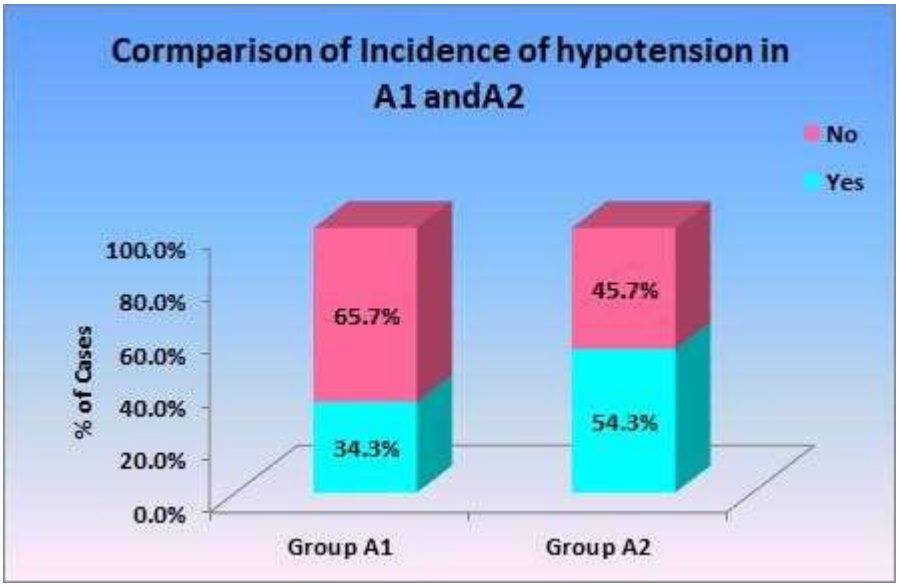

Figure 1: Bar diagrams of incidence of Hypotension observed in the group A1 and A2

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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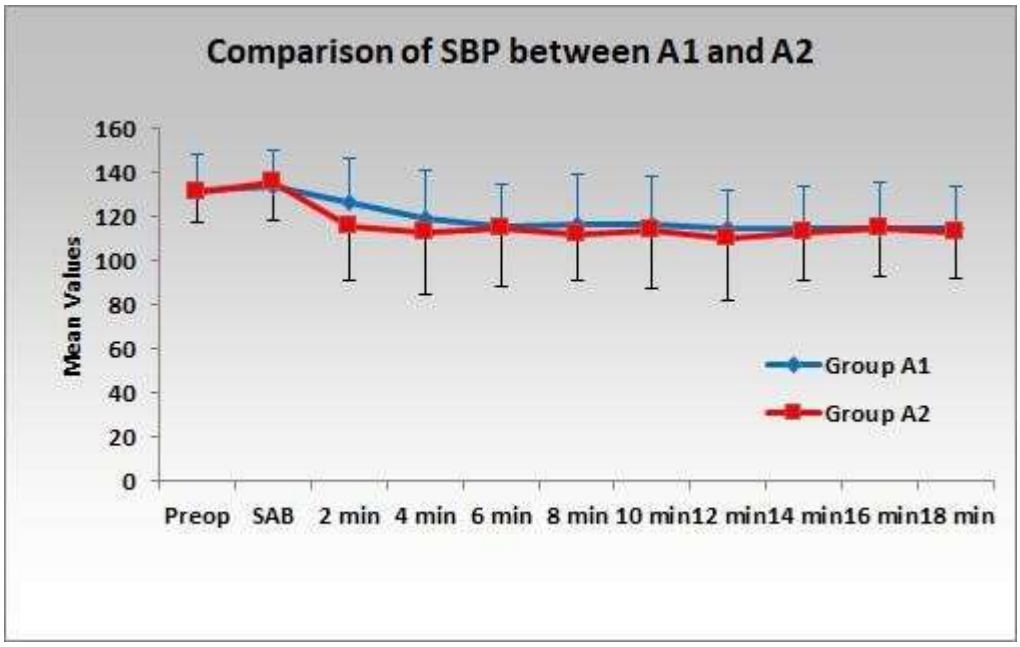

Figure 2: Comparing SBP variation between A1 and A2. Shows SBP variation between the two groups from preoperative value to 18 min after SAB. Although there was drop in SBP in both the groups and comparatively drop was more in group A2 after SAB but the difference was not statistically significant.

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

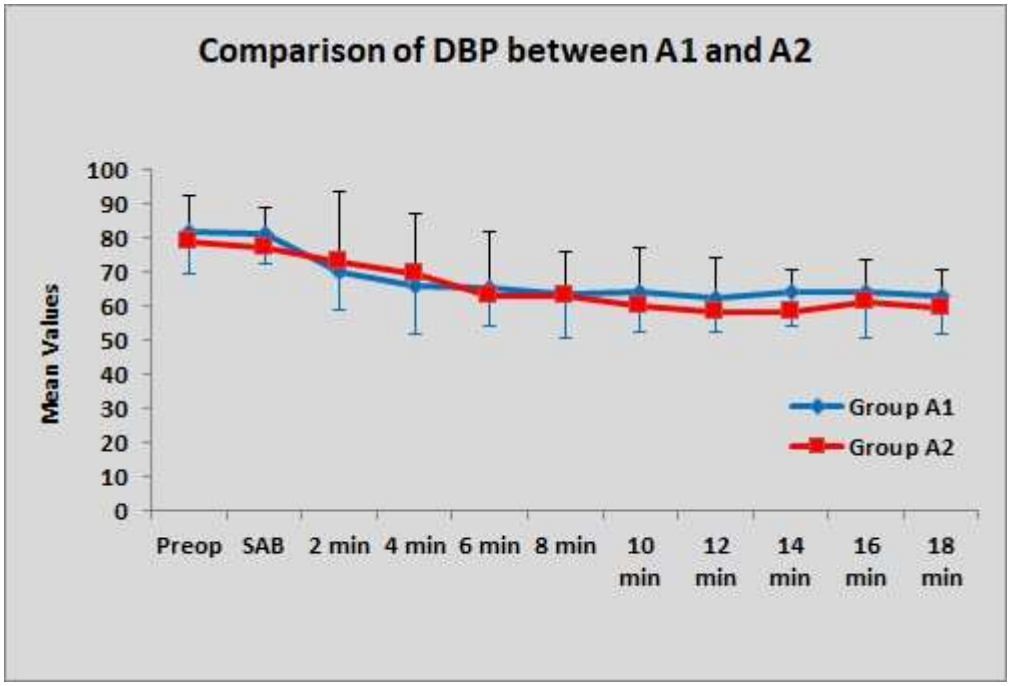

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Figure 3: Comparison of DBP variations between groups A1 and A2. Shows DBP variation between the two groups from preoperative value to 18 min after SAB. There was drop in DBP in both the groups but more in group A2 and it was also statistically significant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

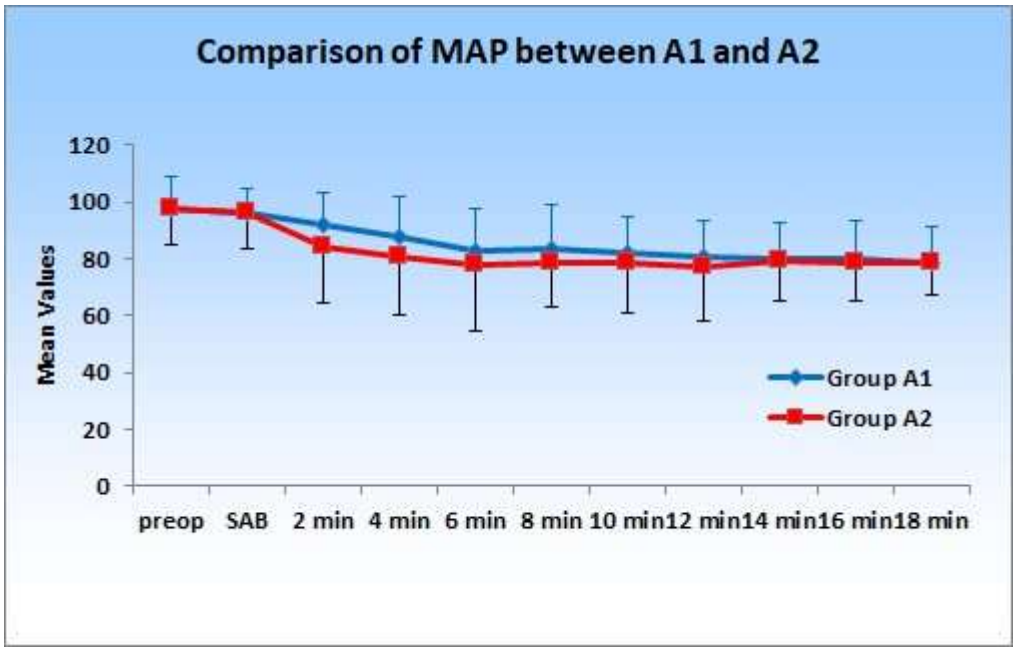

Figure 4: Comparison of MAP variations between groups A1 andA2

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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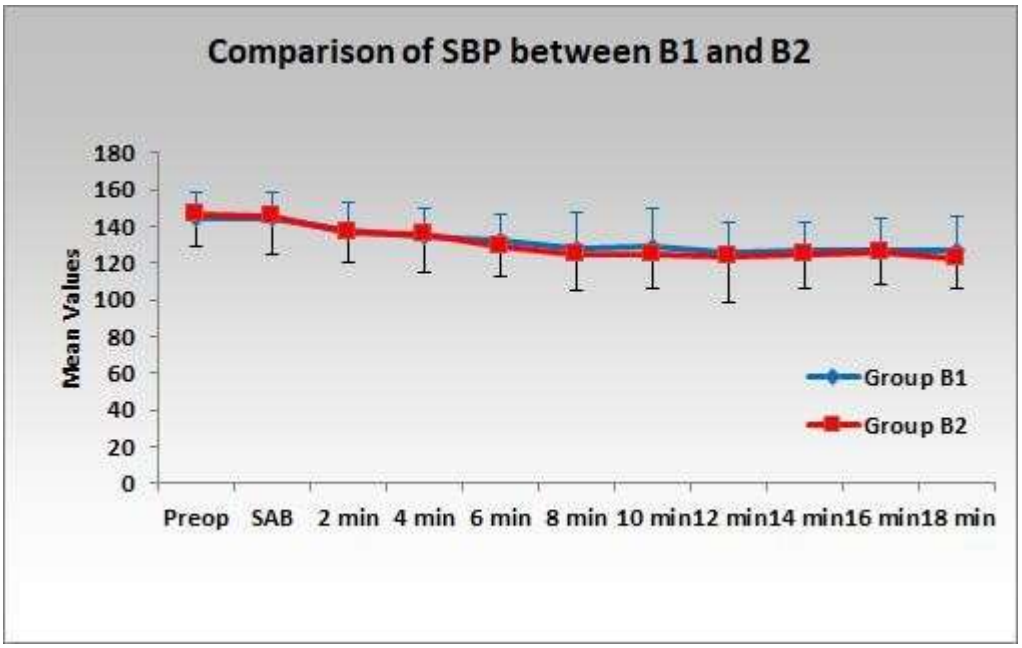

Figure 5: Comparison of SBP variation in B1 and B2. Diagram showing SBP variation between the two groups from preoperative value to 18 minutes after SAB. There was no significant difference between the two groups

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.

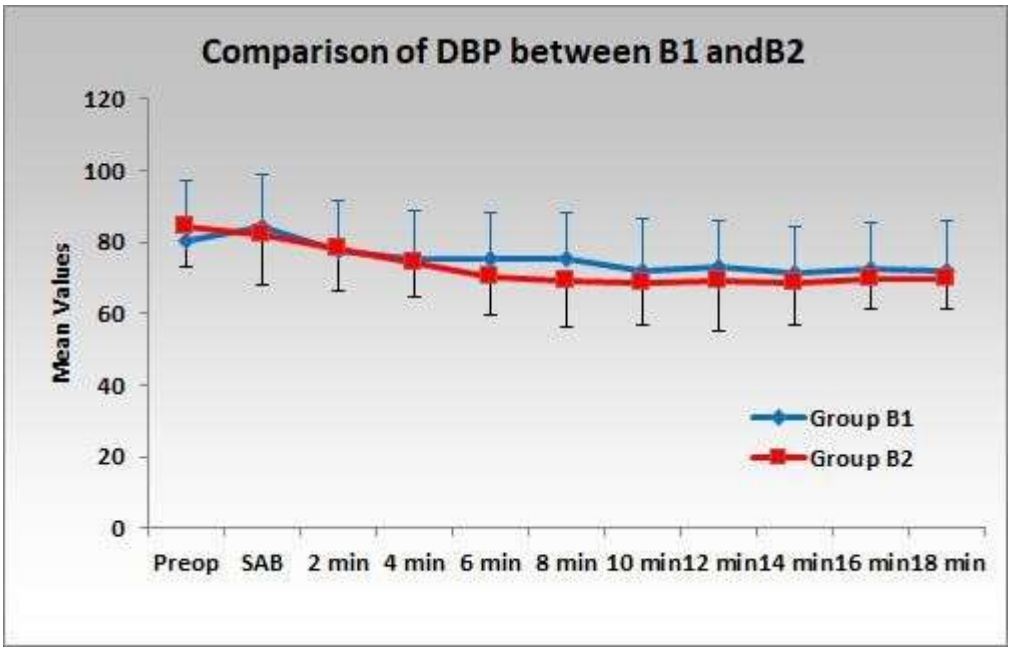

Figure 6: Comparison of DBP variation in B1 and B2. Diagram showing DBP variation between the two groups in non obstetric population. There was fall in DBP in both the groups but the difference was not statistically significant

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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.

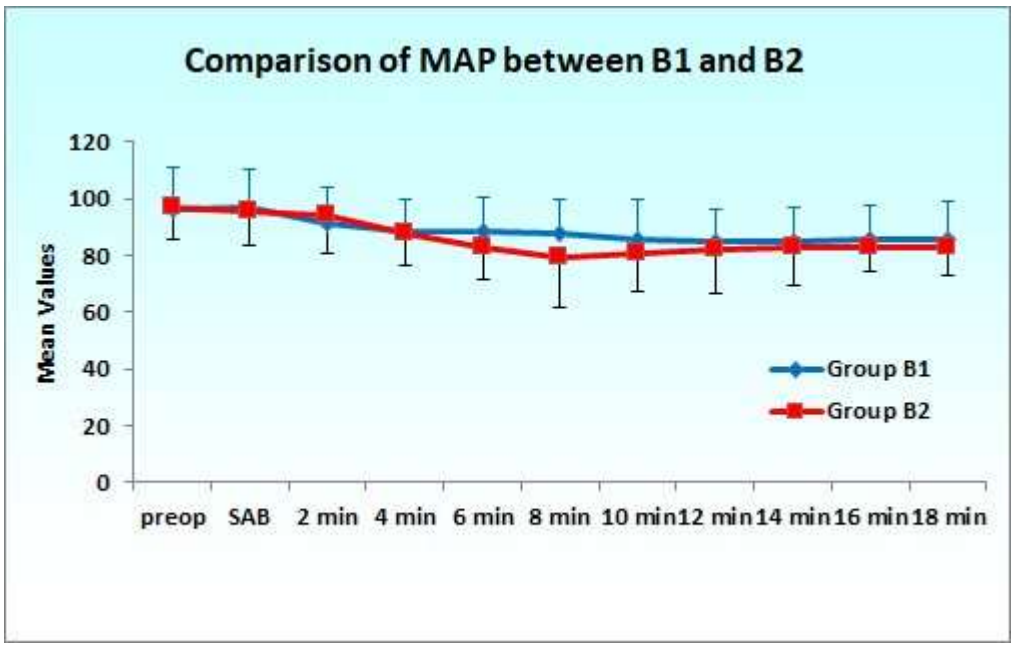

Figure 7: Comparison of MAP variations between B1 and B2 . Diagram showing of fall in MAP in both groups of non obstetric population after SAB. The drop is more in group B2 which is statistically significant with p values= 0.027 and 0.031 at 6 min and 8 min

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.

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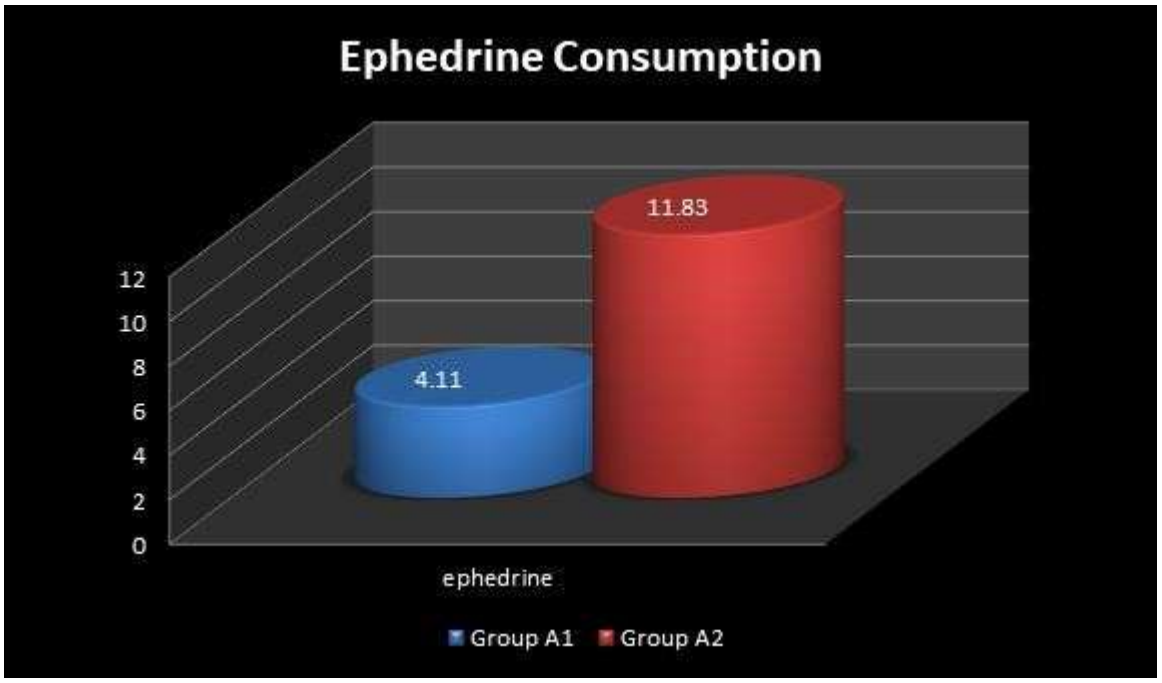

Figure 8: Bar diagrams showing the amount ephedrine consumption in groups A1 and A2 Shows increased requirement of ephedrine in control group among obstetric population which is statistically significant with p value of 0.007. Since its a quantitative data paired t test was applied

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

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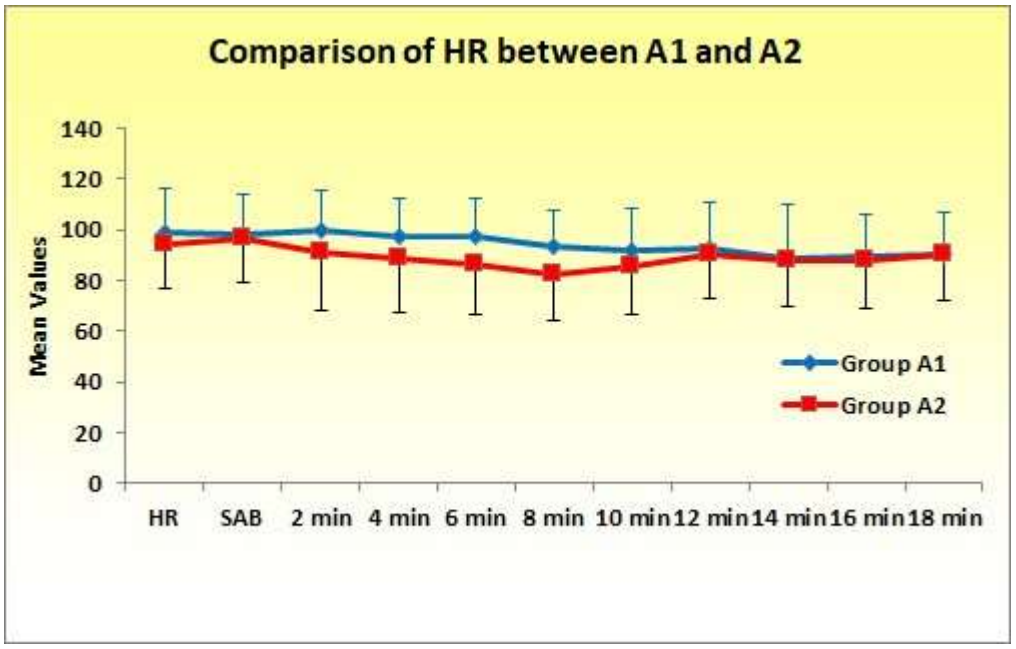

Figure 9: Comparison Heart Rate variation between A1 and A2. Diagram showing Heart Rate variation between the two groups of obstetric population. There is significant drop in HR in group A2 at 2 minutes and 6 minutes

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

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.

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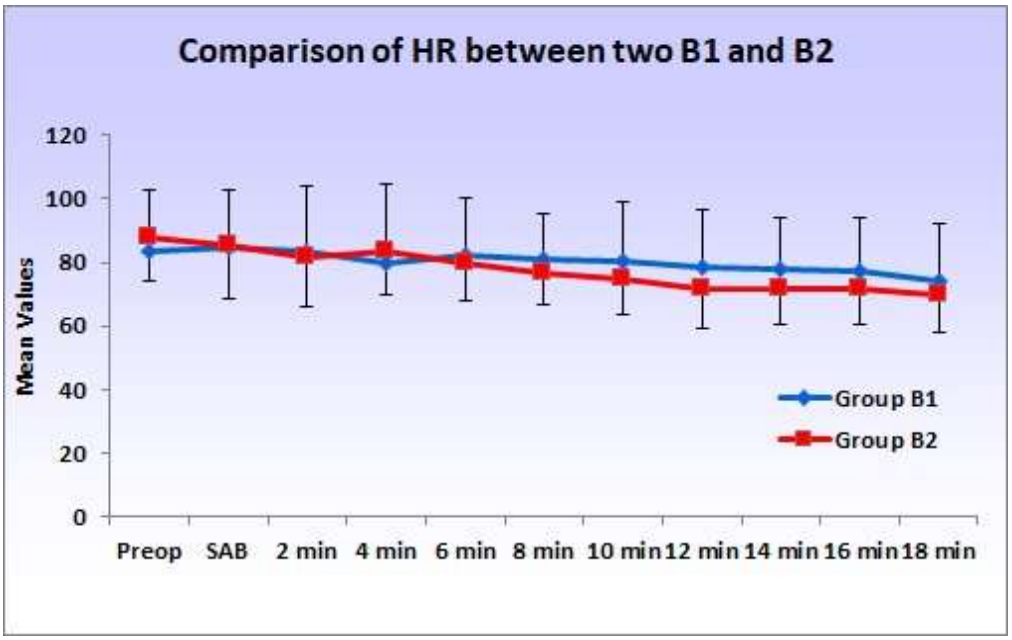

Figure 10: Heart Rate variation between B1 and B2

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.

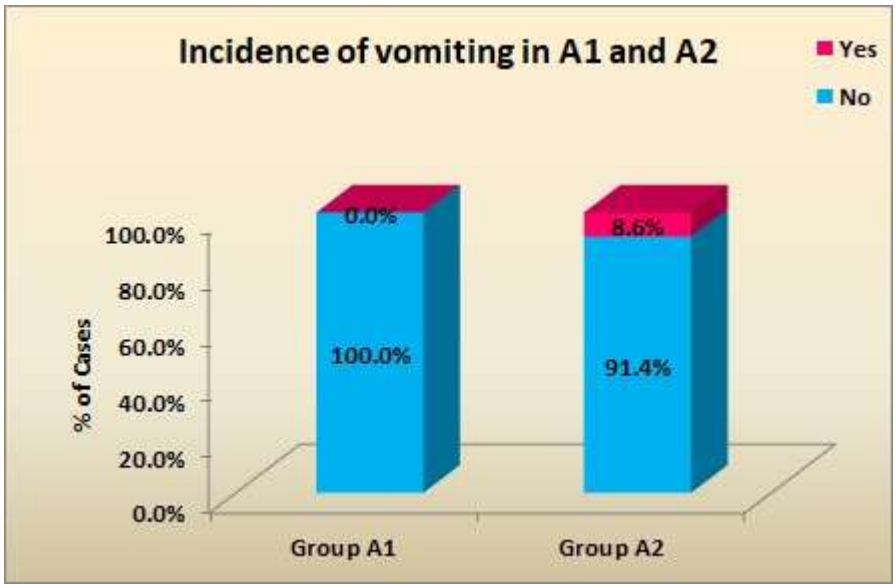

Figure 11: Bar diagrams showing incidence of vomiting in group A1 and A2

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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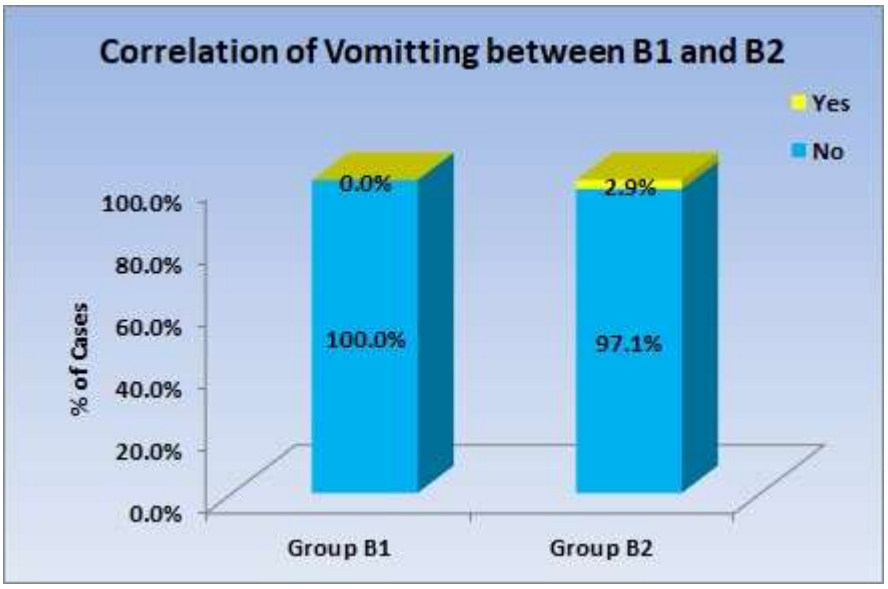

Figure 12: Bar Diagrams showing incidence of vomiting in groups B1 and B2

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

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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.

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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. Our study found that prophylactic administration of ondansetron, a 5HT-3 receptor antagonist produced a insignificant reduction in the incidence of hypotension in both, obstetric and non obstetric population.
2. 5-HT_3 antagonist did not lower the number of patients who required vasopressor for the treatment of hypotension, but the dose of vasopressor used was significantly lower in ondansetron pretreated patients. Ondansetron pretreatment has the potential to avoid harmful fetal effects.
3. None of the patients in the study groups had vomiting. Overall the incidence of vomiting was low (2.9%)

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