Original Article

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Anaesthesia Section

Effect of Palonosetron in the Prevention of Spinal Anaesthesia-induced Hypotension and Bradycardia: A Randomised Controlled Trial

DEVULAPALLI JANARDHANA PRADEEP[1], SANJEEB KUMAR GIRI[2], PARTHA SARATHI MOHAPATRA[3], MOUSUMI DAS[4], LINGARAJ SAHU[5]

ABSTRACT

Introduction: Spinal Anaesthesia (SA) is frequently associated with hypotension, which is due to sympathectomy causing vasodilation, leading to relative hypovolemia. This decrease in venous return to the heart causes a decrease in left ventricular filling pressure, leading to the activation of the Bezold-Jarisch Reflex (BJR), which causes bradycardia. This response is mediated by mechanoreceptors and chemoreceptors present on the heart walls. These chemoreceptors are mediated through serotonin (5-HT). Therefore, the activation of 5-HT3 receptors at sensory vagal nerve endings in the heart causes hypotension and bradycardia.

Aim: To assess the efficacy of Palonosetron in attenuating spinal anaesthesia-induced hypotension and bradycardia.

Materials and Methods: The trial was a parallel-design, randomised, double-blind controlled trial conducted over two years, from February 2021 to August 2022 in the Department of Anaesthesiology, Kalinga Institution of Medical Sciences (KIMS), Bhubaneswar, Odisha, India, among patients undergoing spinal anaesthesia for various surgeries. The patients were divided into two groups based on the type of medication received: Group A-Palonosetron group and Group B- the saline group. Computer-generated random number generator software was used for randomisation. At a 1:1 ratio, 150 patients were chosen (75 in each group). Baseline assessment of haemodynamic parameters was performed, followed by continuous monitoring. The drug was administered 10 minutes prior to spinal anaesthesia, and the haemodynamic parameters (Heart Rate [HR], Systolic Blood Pressure [SBP], Diastolic Blood Pressure [DBP], and Mean Arterial Pressure [MAP]) were monitored. Continuous variables are expressed as mean±Standard Deviation (SD). The Student's t-test was used to compare the difference between the two groups, and categorical variables are expressed as frequency and percentage, with comparisons done using the Chi-square test. A p-value of <0.05 was considered statistically significant.

Results: The mean age of Group A and Group B was 40.88 and 42.14, respectively. Significant haemodynamic changes (hypotension) were observed following induction in Group B (28 [37.3%]) compared to Group A (9 [12%]). Consumption of vasopressors and intravenous (i.v.) fluids was significantly higher in Group B compared to Group A. The incidence of bradycardia in Group A and Group B was 15 (20%) and 18 (24%), respectively. Postoperative Nausea and Vomiting (PONV) in Group A and Group B were 3 (4%) and 8 (10.7%), respectively.

Conclusion: Based on the present study, the prophylactic administration of 0.075 mg Palonosetron 10 minutes before subarachnoid block is effective in attenuating the incidence of spinal anaesthesia-induced hypotension and bradycardia. There is also decreased consumption of vasopressors and a lower incidence of PONV.

Keywords: 5-HT3 antagonists, Subarachnoid block, Vasopressors

INTRODUCTION

The SA is one of the most common methods of providing perioperative anaesthesia. The advantages are that it is easy to perform, the onset is quick, and it saves a lot of time in a busy operating schedule. Therefore, it is popularly used for infraumbilical surgeries. In spinal anaesthesia, due to sympathectomy, it is frequently associated with hypotension [1]. Sympathectomy causes vasodilation, leading to relative hypovolemia. This decreases venous return to the heart. The decrease in venous return causes a decrease in left ventricular filling pressure, which activates the BJR, causing bradycardia [2]. Hypotension, along with bradycardia, causes a decrease in cardiac output, which is a life-threatening complication and requires aggressive treatment. Studies have shown that the incidence of hypotension in SA is approximately 40% in non obstetric patients and 80% in obstetric patients [1,3]. Hypovolemia stimulates the mechanoreceptors and chemoreceptors present on the heart walls, causing the activation of the BJR. These chemoreceptors are mediated through serotonin (5-HT). Activation of the 5-HT3 receptor at sensory vagal nerve endings in the heart causes hypotension and bradycardia [4]. Various studies have been done with 5-HT3 receptor antagonists to prevent hypotension and bradycardia [5-7]. Additionally, Eldaba AA and Amr YM showed that granisetron 1 mg pre-spinal anaesthesia significantly decreased the occurrence of hypotension and bradycardia and decreased the need for vasopressors compared to a placebo group during caesarean delivery [8]. Hence, we hypothesised that 5-HT3 antagonists attenuate spinal anaesthesia-induced hypotension and bradycardia. Second-generation 5-HT3 receptor antagonist, Palonosetron, has been found to have more effective antiemetic properties. It has a higher affinity for the receptors than the first-generation 5-HT3 antagonists like ondansetron and granisetron [9]. Thus, the purpose of the present study was to evaluate the effect of Palonosetron in attenuating spinal anaesthesia-induced hypotension and bradycardia.

MATERIALS AND METHODS

The trial was a parallel-design, randomised, double-blind controlled trial that lasted two years, from February 2021 to August 2022, in the Anaesthesiology and Critical Care Department, Kalinga Institution of

Medical Sciences, Bhubaneswar, Odisha, India, among patients undergoing spinal anaesthesia for various surgeries. After obtaining approval from the Institutional Research and Ethics Committee (KIIT/KIMS/IEC/414/2020), the trial was entered in the Clinical Trial Registry India (CTRI/2021/01/030524). Then the study was conducted after obtaining informed written consent from the patients.

Inclusion criteria: A total of 150 patients aged 18-65 years from either gender, of the American Society of Anaesthesiologists (ASA) Grade-I and II, posted for various elective surgeries under spinal anaesthesia were included in the study.

Exclusion criteria: Patients with hypertension, diabetes, obesity, patients on selective serotonin reuptake inhibitors, parturients, and those who refused spinal anaesthesia were excluded from the study.

The primary outcome measure: HR, SBP, DBP, MAP were measured and recorded at 3-minute intervals until 60 minutes after spinal anaesthesia.

The secondary outcome measure: Amount of vasopressors and vagolytic requirements.

Sample size calculation: The sample size was calculated using the proportions of bradycardia between the two groups based on the study done by Raghu K et al., [10]. Patients were randomly assigned to one of two groups, Group A (Drug) or Group B (Placebo), each with 75 patients.

Group A: Patients were given Palonosetron 1.5 mL (0.075 mg) diluted up to 4 mL with distilled water i.v.

Group B: Patients were given 4 mL of distilled water i.v.

A computer-generated randomisation list was prepared and used for randomisation. The primary investigator and patients were blinded to the interventional agent.

Study Procedure

According to conventional Nil Per Oral (NPO) standards, all patients were kept on a fast after preoperative evaluation. Baseline HR, non invasive blood pressure, and pulse oximetry (SpO_2) measurements were obtained in the operating room. A peripheral 18-G intravenous cannula (IV cannula) was attached, and 10 mL/kg of lukewarm Ringer's lactate solution was preloaded. The interventional agent was then injected i.v. 10 minutes prior to administering spinal anaesthesia. With the patient in the sitting position, a lumbar puncture was performed in the L3-L4 intervertebral area (midline approach) with a 25 G Quincke spinal needle using full aseptic measures. 3 mL of 0.5% hyperbaric bupivacaine was injected over a 15-second period after obtaining a clear and free flow of CSF. The patients were immediately placed in a supine position. The table position was adjusted to achieve a sensory block level up to T8.

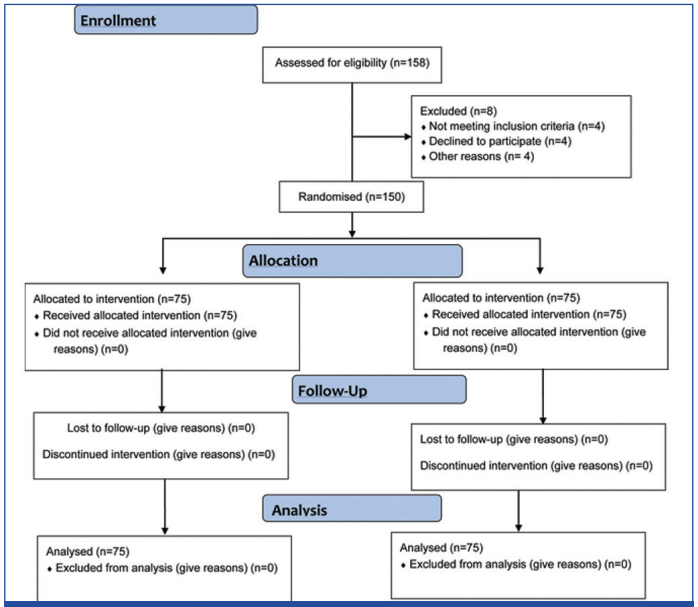
At three-minute intervals, Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Mean Arterial Pressure (MAP) were monitored and recorded for 60 minutes after spinal anaesthesia. A reduction in SBP of ≤20% from the baseline was considered hypotension, and 6 mg of ephedrine was administered intravenously to treat it. Intravenous atropine 0.6 mg was used to treat bradycardia (HR <50 beats/min). The amount of vasopressors, vagolytics, and intravenous fluids required was calculated and recorded. The incidence of Postoperative Nausea and Vomiting (PONV) was also recorded. Patients were transferred to a postanaesthesia care facility and observed until the sensory block resolved in two segments.

STATISTICAL ANALYSIS

Continuous variables are expressed as mean±SD, and categorical variables are presented as frequency and percentage. To determine whether the difference between the two groups is significant, a Student's t-test is used for continuous variables, while a Chi-square test is used for categorical variables. A p-value of <0.05 is considered statistically significant.

RESULTS

[Table/Fig-1] shows the CONSORT flowchart. In terms of demographic variables, both groups in the current study were comparable, including sex, Body Mass Index (BMI), age, and ASA grades [Table/Fig-2]. [Table/Fig-3-6] represent HR, SBP, DBP, and MAP at three-minute intervals up to 60 minutes, respectively, between the groups. [Table/Fig-7] represents the incidence of hypotension, bradycardia, and the requirement of vasopressors between the groups. There was a significant difference in the reduction of MAP from the baseline in Group-B compared to Group-A (mean 19.04±12.51 vs. 15.30±13.37, p=0.022). Hypotension developed in nine patients in Group-A (12%) and 28 patients in Group-B (37%), which was statistically significant (p<0.001). The requirement for vasopressors was higher in Group-B compared to Group-A (<0.008). [Table/Fig-8] shows a comparison of the incidence of bradycardia and the requirement of atropine between the groups. There was no statistically significant difference in the occurrence of bradycardia between the groups. Fifteen patients in Group-A (20%) developed bradycardia, whereas it was 18 in Group-B (24%) (p=0.554). Atropine was required for three patients in Group-B and one in Group-A. [Table/Fig-9] shows the requirement of intravenous fluids between the two groups. The requirement for intravenous fluids was higher in Group-B compared to Group-A (p<0.028). Three patients from Group-A and eight from Group-B developed PONV.



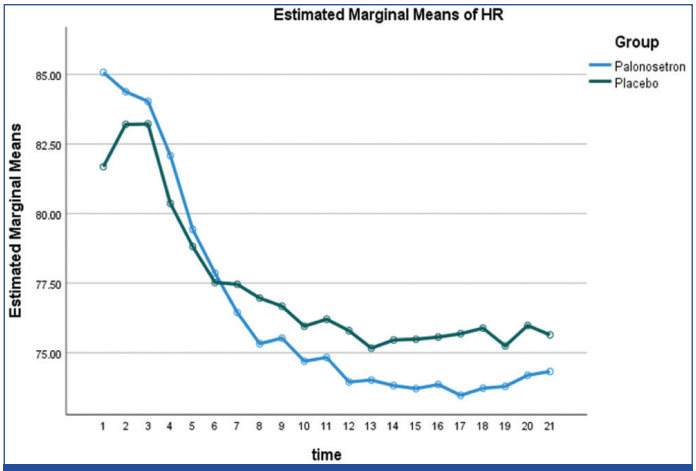
[Table/Fig-1]: CONSORT flowchart.

Variables	Group-A n=75	Group-B n=75	p-value
Gender (M:F)	66:09	52:23	0.005
Age (years) (mean±SD)	40.88±13.17	42.14±13.09	0.547
Weight (kg) (mean±SD)	66.067±9.39	61.40±10.14	0.004
Height (cm) (mean±SD)	169.08±6.24	165.83±7.33	0.004
BMI (kg/m^2) (mean±SD)	21.36±2.89	20.75±3.16	0.221
ASA Grade (I:II)	62:13	62:13	0.494

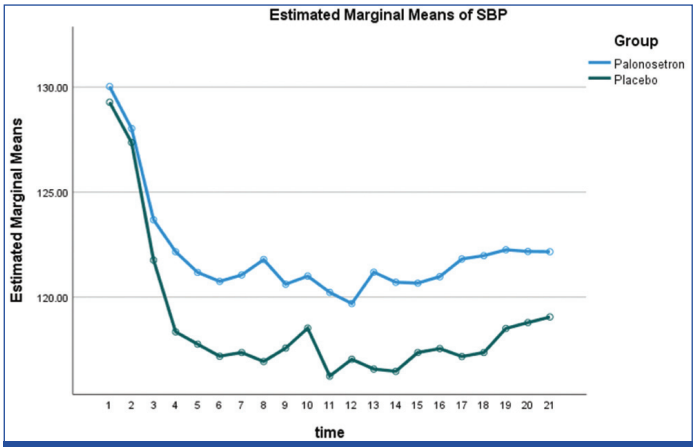
[Table/Fig-2]: Comparison of demographic variables and ASA status between two groups. The t-test was used for statistical analysis. Statistically significant at p<0.05.

In [Table/Fig-3], the x-axis represents time intervals (1 to 21, with 1 being the baseline and 21 being the 60th minute), with each interval equivalent to three minutes. The graph covers a total of 60 minutes. At each time interval, from the baseline to the 60th minute, there was no significant difference in the mean HR between the two groups (p>0.05). Statistical analysis was performed using the t-test, with p<0.05 considered statistically significant.

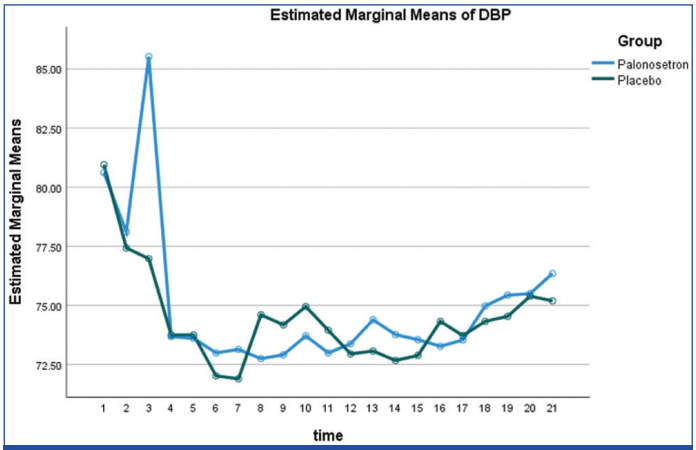
In [Table/Fig-4], the x-axis represents time intervals (1 to 21, with 1 being the baseline and 21 being the 60th minute), with each



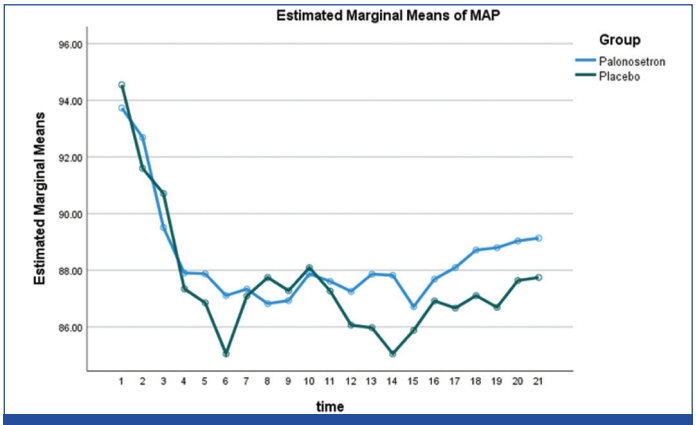
[Table/Fig-3]: Representing the Heart Rate (HR) of the study population at different time intervals.



[Table/Fig-4]: Representing the Systolic Blood Pressure (SBP) of the study population at different time intervals.



[Table/Fig-5]: Representing the Diastolic Blood Pressure (DBP) of the study population at different time intervals.



[Table/Fig-6]: Representing the mean blood pressure of the study population at different time intervals.

Variables		Group-A	Group-B	p-value
Bradycardia, n (%)		15 (20)	18 (24)	0.554
Hypotension, n (%)		9 (12)	28 (37)	0.001
Haemodynamic variables (baseline-lowest values)				
HR (beats/min)		18.00±11.00	15.00±9.15	0.131
SBP (mmHg)		19.32±11.32	24.50±16.80	0.057
DBP (mmHg)		15.08±9.58	19.46±15.20	0.094
MAP (mmHg)		15.30±13.37	19.04±12.51	0.022
No. of doses of required vasopressure	1	6	11	0.008
	2	2	9	
	3	1	4	
	4	0	2	
	5	0	2	

[Table/Fig-7]: Incidence of bradycardia and hypotension, requirement of vasopressors between the groups.
Values are mean±SD or number of patients (%)
Chi-square test was used for statistical analysis. p<0.05, indicates statistical significance

Variables	Group-A n (%)	Group-B n (%)	p-value
Bradycardia	15 (20%)	18 (24%)	0.554
Atropine required	1 (1.3%)	3 (4%)	

[Table/Fig-8]: Comparison of incidence of bradycardia and requirement of atropine between the groups. Statistical analysis done with Chi-square test.

No of units used (i.v. fluids) (1 unit=500 mL)	Group-A n (%)	Group-B n (%)	p-value
1	3 (4%)	0 (0%)	0.028
2	66 (88%)	58 (77%)	
3	6 (8%)	17 (22.6%)	

[Table/Fig-9]: Intravenous (i.v.) fluids requirement in between the two groups.
The Chi-square test was used to do statistical analysis. p<0.05 being taken as statistically significant

interval equivalent to three minutes. The graph covers a total of 60 minutes. There was no significant difference in the mean SBP between the two groups at each time interval, from the baseline to the 60th minute (p>0.05). Statistical analysis was performed using the t-test, with p<0.05 considered statistically significant.

In [Table/Fig-5], the x-axis represents time intervals (1 to 21, with 1 being the baseline and 21 being the 60th minute), with each interval equivalent to three minutes. The graph covers a total of 60 minutes. At the 24th minute (at point 9), there was a significant difference in the mean DBP between the two groups (p=0.015). Statistical analysis was performed using the t-test, with p<0.05 considered statistically significant.

In [Table/Fig-6], the x-axis represents time intervals (1 to 21, with 1 being the baseline and 21 being the 60th minute), with each interval equivalent to 3 minutes. The graph covers a total of 60 minutes. It was found that at the 12th, 21st, and 27th minutes (at points 5, 8, 10), there was a significant difference in MAP between the two groups (p=0.02, 0.009, and 0.015, respectively). Statistical analysis was performed using the t-test, with p<0.05 considered statistically significant.

DISCUSSION

Although spinal anaesthesia is considered a safe treatment, problems such as hypotension and bradycardia may occur. Hypotension is due to sympathectomy [1]. Hypotension causes vasodilation, leading to relative hypovolemia. This decreases venous return to the heart, which causes a decrease in left ventricular filling pressure, leading to the activation of the Bezold-Jarisch Reflex (BJR) and bradycardia [2]. This reflex is mediated by the mechanoreceptors and chemoreceptors present on the heart walls. These chemoreceptors are mediated through serotonin (5HT). Activation of the 5-HT3 receptor at sensory vagal nerve endings in the heart causes hypotension and bradycardia

[4]. 5-HT3 receptor antagonists have been found to attenuate spinal anaesthesia-induced hypotension and bradycardia [5-7]. The current study was designed to investigate the effect of Palonosetron (a 5-HT3 receptor antagonist) in the prevention of spinal anaesthesia-induced hypotension and bradycardia.

Regarding haemodynamics, the results of the present study showed a higher incidence of hypotension in the placebo group (37%) compared to the Palonosetron group. The consumption of vasopressors and intravenous fluids was significantly higher in the placebo group compared to the Palonosetron group. Regarding bradycardia, there was no significant difference between the placebo group and the Palonosetron group. The incidence of bradycardia was 15 patients in the Palonosetron group and 18 patients in the placebo group, with one patient in the Palonosetron group and three patients in the placebo group requiring atropine. The incidence of Postoperative Nausea and Vomiting (PONV) was 3 (4%) in the Palonosetron group and 8 (10.7%) in the placebo group. These results are comparable to previously conducted studies.

In a study conducted by Sood S et al., one group of patients received 0.25 mg of intravenous Palonosetron, while the other group received a placebo [11]. Palonosetron was injected prior to spinal anaesthesia. They found a significant reduction in MAP (Palonosetron vs. placebo) at 20 minutes (89.30±10.90 vs. 76.78±8.83 mmHg, p=0.031), at 25 minutes (88.88±10.96 vs. 78.76±9.16 mmHg, p=0.001), and at 30 minutes (88.94±10.52 vs. 77.85±9.65 mmHg). In the present study, the interventional group received 0.075 mg of Palonosetron. The reduction of Mean Arterial Pressure (MAP) at 12 minutes was 87.87±9.67 in the Palonosetron group compared to 86.85±12.66 in the placebo group (p=0.02). At 21 minutes, the MAP was 86.82±9.33 mmHg in the Palonosetron group and 87.74±14.13 mmHg in the placebo group (p=0.009). At 27 minutes, the MAP was 87.87±9.58 mmHg in the Palonosetron group and 88.09±11.47 mmHg in the placebo group (p=0.015). Thus, both studies yielded comparable results in terms of hypotension, despite the different drug dosages used.

In a study by Sahoo T et al., on 52 parturients undergoing elective caesarean section, patients were randomly assigned to receive 4 mg of ondansetron or normal saline before spinal anaesthesia. They found a significant reduction in MAP at 5 minutes (88±11.7 vs 82.2±10.5 mmHg, p=0.038) and six minutes (87.5±11.3 vs 80.4±10.8 mmHg, p=0.025) in the ondansetron group compared to the placebo group [12].

In another study by Shah SARA et al., involving 100 patients, the interventional group received 8 mg of ondansetron before spinal anaesthesia [13]. They found that the incidence of hypotension was 34 (68%) in the placebo group and 23 (46%) in the ondansetron group. Similarly, in the present study, the incidence of hypotension was significantly higher in the placebo group with 28 (37%) cases compared to the Palonosetron group with 9 (12%) cases.

Ankita A et al., conducted an RCT among 150 parturients, with one group receiving 4 mg of ondansetron and the other group receiving normal saline 10 minutes before the initiation of subarachnoid block [14]. They studied haemodynamic parameters from the induction of the drug until the delivery of the baby. They found that the decrease in SBP, DBP, and MAP was significantly lower in the ondansetron group compared to the placebo group. They also observed no significant change in HR between the groups (p=0.144). The overall dose of vasopressors was considerably lower in the ondansetron group compared to the placebo group (p<0.05). The present study's results align with Ankita A et al.,'s study regarding blood pressure, HR, and the requirement for vasopressors [14].

Although the occurrence of bradycardia did not significantly differ between the groups, a fall in HR was more common in the placebo group. Additionally, the consumption of vasopressors was higher in the placebo group. Despite using a first-generation 5-HT3 antagonist, Al Zahraa AA et al., found results similar to the present study in terms of hypotension, bradycardia, and vasopressor requirement. They conducted an RCT on 60 parturients for caesarean sections, where parturients were randomly assigned to receive either ondansetron 4 mg or normal saline prior to subarachnoid block. They found a significantly higher incidence of Postoperative Nausea and Vomiting (PONV) in the placebo group (18 [60%]) compared to the ondansetron group (6 [20%]; p=0.002) [15]. Their results can be comparable to the present study. In the present study, 3 (4%) patients from the Palonosetron group and 8 (10.7%) patients from the placebo group complained of Postoperative Nausea and Vomiting (PONV). Despite the present study using a second-generation 5-HT3 antagonist as the interventional drug, the results show that the incidence of PONV is comparable between the Palonosetron and placebo groups. Additionally, they found a higher incidence of hypotension and a greater requirement for vasopressors in the placebo group compared to the ondansetron group, which aligns with the findings of the present study.

Marashi SM et al., compared two different doses of ondansetron with placebo [16]. They enrolled 210 patients scheduled for elective spinal anaesthesia operations and randomly assigned them to one of three groups, with the interventional groups receiving ondansetron 6 mg and 12 mg, 5 minutes before spinal anaesthesia. The placebo group received normal saline. They found that Heart Rate (HR) was significantly different between the interventional groups and the control group. In the placebo group, 10 (14%) patients required intravenous atropine (p=0.02) due to bradycardia. Mean Arterial Pressure (MAP) was statistically different between the ondansetron groups and the placebo group. In the placebo group, 12 patients required vasopressors, which was statistically significant compared to the ondansetron groups (p=0.04). They concluded that ondansetron successfully attenuates spinal anaesthesia-induced bradycardia and hypotension. Their study results were similar to the present study regarding hypotension. However, the present study found no significant difference in bradycardia between the groups, which contradicted their findings.

Choi JJ et al., in their study on 60 patients undergoing lower limb surgery, randomly assigned patients to receive either Palonosetron (0.075 mg) or normal saline before performing subarachnoid block [17]. They found no significant difference in blood pressure or HR between the groups and concluded that Palonosetron (0.075 mg) might not attenuate hypotension induced by spinal anaesthesia. The present study has contradictory results compared to Choi JJ et al., even though both studies used the same dose of Palonosetron. The incidence of hypotension in either group in their study was 40%. However, in the present study, the incidence of hypotension was 12% in the Palonosetron group and 37% in the placebo group.

Chaudhury J et al., conducted a study with 126 female patients (ASA I and II physical status) undergoing abdominal hysterectomy under spinal anaesthesia [18].

Patients were randomly allocated into three groups: placebo, receiving granisetron 1 mg, or receiving Palonosetron 0.075 mg intravenously before the induction of spinal anaesthesia. They found that there was no significant difference in Mean Arterial Pressure (MAP) and Heart Rate (HR) among the three groups. In contrast to their study, the present study showed a significant difference in the reduction of MAP from baseline in the placebo group compared to the Palonosetron group, despite both studies using the same dose of Palonosetron. However, there was no significant difference in HR between the two groups, which is consistent with their study.

Limitation(s)

One limitation of the present study was that the patients were monitored using non invasive Blood Pressure (NIBP) measurement, whereas invasive blood pressure monitoring would have been more reliable. Additionally, the use of sympathomimetics like ephedrine

for treating hypotension, which has a tendency to raise both blood pressure and HR, could have masked the prevalence of bradycardia.

CONCLUSION(S)

Spinal anaesthesia is commonly associated with complications such as hypotension and bradycardia due to sympathetic blockade. The reduced preload to the heart triggers the Bezold-Jarisch reflex, causing bradycardia. This reflex is mediated by serotonin-sensitive (5HT3) vagal nerve terminals in the heart wall. Therefore, the prophylactic administration of 0.075 mg of Palonosetron (a 5HT3 antagonist) intravenously 10 minutes before subarachnoid block is effective in attenuating the incidence of spinal anaesthesia-induced hypotension and bradycardia. There was also a lower consumption of vasopressors and a lower incidence of Postoperative Nausea and Vomiting (PONV).

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate, Department of Anaesthesiology, KIMS, Bhubaneswar, Odisha, India.
2. Assistant Professor, Department of Anaesthesiology, KIMS, Bhubaneswar, Odisha, India.
3. Associate Professor, Department of Anaesthesiology, KIMS, Bhubaneswar, Odisha, India.
4. Associate Professor, Department of Anaesthesiology, KIMS, Bhubaneswar, Odisha, India.
5. Professor, Department of Anaesthesiology, KIMS, Bhubaneswar, Odisha, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Mousumi Das,
Associate Professor, Department of Anaesthesiology, KIMS, PBMH,
Bhubaneswar-751024, Odisha, India.
E-mail: mousumi.das1503@gmail.com

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