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Research Article

A PROSPECTIVE OBSERVATIONAL STUDY OF INTRAVENOUS ONDANSETRON AND PALONOSETRON IN ATTENUATING HYPOTENSIVE RESPONSE FOLLOWING SPINAL ANESTHESIA IN PATIENTS UNDERGOING ELECTIVE CESAREAN SECTION

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ABSTRACT

Objective: To compare the efficacy of prophylactic administration of intravenous ondansetron and palonosetron in attenuating hypotensive response following spinal anesthesia in patients undergoing elective cesarean section.

Methods: This was a comparative study in which 84 patients aged 18–35 years of American Society of Anesthesiologists physical status II, scheduled for elective cesarean section under spinal anesthesia (SA) were included based on predefined inclusion and exclusion criteria. 84 patients undergoing elective cesarean sections were divided into two groups to receive either ondansetron or palonosetron before SA. Vital signs were monitored, with interventions for hypotension or bradycardia. Data on vital signs, vasopressor use, neonatal Apgar scores, and post-operative symptoms were collected and analyzed. For statistical purposes, a *P* value less than 0.05 was taken as statistically significant.

Results: The mean ages and body mass indexes (BMIs) of the groups were similar, with no significant statistical difference (p=0.674 and p=0.3583, respectively). Heart rates, systolic and diastolic blood pressures showed minor differences, but only a few instances were statistically significant. Mean arterial pressures differed significantly at multiple intervals, but no clinical hypotension was observed. S_pO2 levels remained stable and comparable in both groups. Average phenylephrine usage was also similar, with no significant difference. The incidence of hypotension, sedation scores, and incidence of bradycardia were comparable. Neonatal outcomes, measured by APGAR scores, showed no significant difference, indicating similar newborn health status in both groups.

Conclusion: Prophylactic ondansetron, as well as palonosetron, were equally effective in reducing the incidence and severity of hypotension in healthy parturients following spinal anesthesia with hyperbaric bupivacaine for elective LSCS.

Keywords: Ondansetron, Palonosetron, Bupivacaine, LSCS, Neonatal outcome.

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INTRODUCTION

Spinal anesthesia (SA) is considered the gold standard for elective cesarean section whenever appropriate [1]. This is a simple, fastly performed, powerful, and reliable technique. SA is the standard anesthetic method for cesarean section with certain advantages over general anesthesia like reduced stress response to surgery, adequate motor blockade for the surgical procedure, and post-operative analgesia. Although it is considered safer, it has many adverse effects, including nausea, vomiting, bradycardia, and other dysrhythmias [2]. Among these cardiovascular complications are predominant. Large surveillance studies typically observed an incidence of hypotension of around 33% and bradycardia of about 13% in non-obstetric population [3].

However, in obstetrics cases, spinal anesthesia indeed requires a sensory block up to T5, which always leads to an extended sympathetic blockade and hypotension occurring in 55–90% of cases, despite the partial left lateral decubitus (with the objective of limiting aortocaval compression caused by the gravid uterus) [4]. This hypotension is associated with a decrease in cardiac output and uteroplacental flow, which may induce fetal morbidity. It is crucial to prevent/or treat it quickly and effectively. The main treatment is the vascular filling with crystalloid/colloids and the use of vasopressors [5]. However, many studies showed that it was ineffective and a recent review found that no intervention reliably prevents hypotension during spinal anesthesia for cesarean section. The pathophysiologic mechanism is decreased systemic vascular resistance and central venous pressure from the sympathetic block with vasodilatation [6]. Bradycardia may be due to relative dominance of the parasympathetic system, increased baroreceptor activity, or due to the Bezold–Jarisch reflex (BJR) [7]. The latter is triggered by stimulation of intracardiac receptors, and its consequences include bradycardia, vasodilatation, and hypotension. Receptors triggering the BJR are mechanoreceptors located in the heart walls, which participate in systemic responses to hypervolemia and hypovolemia [8].

The receptors in the walls of the four cardiac chambers are the non-encapsulated terminals of the C-fiber afferents and are heterogeneous in terms of their responsiveness to mechanical (pressure, inotropism, and volume) and chemical (veratrum alkaloids, adenosine tri-phosphate, serum amidine derivatives, capsaicin and venoms from snakes, insects, and marine animals) stimuli, and most respond to veratrum alkaloids, the classic pharmacologic stimulus for the BJR. They also include chemoreceptors sensitive to serotonin (5-HT3 receptors) [9]. 5-HT3 receptors vary from other serotonin receptors, which are mainly coupled to G-protein [10].

It seems that both types of receptors are involved in the induction of hypotension and bradycardia after spinal blockade. Although mechanoreceptors located in all cardiac chambers are normally sensitive to distension, diminished venous return of blood, as observed after spinal block, induces deformation of the cardiac wall, resulting in irritation of mechanoreceptors and activation of the BJR [11]. Chemoreceptors are activated by serotonin released from activated thrombocytes. Animal studies suggest that serotonin may be an

important factor inducing BJR in cases of decreased blood volume, and the mechanism of triggering the reflex depends on the activation of peripheral 5-HT3 receptors located in intracardiac vagal nerve endings by serotonin. Yamano *et al*. demonstrated that 5-HT3 receptor blockade antagonizes BJR induced by serotonin administration in rats [12].

Because spinal blockade may lead to relative hypovolemia, researchers have hypothesized that hemodynamic changes due to such a blockade may be attenuated with 5-HT3 receptor antagonists such as ondansetron and palonosetron. Previous studies of the general population and pregnant women in whom SA was performed for the cesarean section have revealed that the administration of ondansetron before the blockade may be an effective method to attenuate the decrease in blood pressure. Moreover, previous studies also successfully showed that administration of these anti-5HT3 groups of drugs can prevent post-operative nausea and vomiting (PONV) without affecting fetal outcome [13].

Therefore, we have performed a prospective observational study to compare the efficacy of prophylactic administration of intravenous ondansetron and palonosetron combined with rapid crystalloid pre-loading to reduce maternal hypotension during cesarean delivery. We have also assessed the effects of the same on neonatal outcomes after delivery.

METHODS

This was a comparative study in which 84 patients aged 18–35 years of American Society of Anesthesiologists (ASA) physical status II, scheduled for elective cesarean section under SA were included on the basis of predefined inclusion and exclusion criteria. The study was conducted in the department of anesthesiology of a tertiary care medical college. Written and informed consent was obtained from all the cases.

All patients posted for operation fasted for 6–8 h, but sips of clear fluid were allowed till 2 h before surgery. On arrival in the operating room (OR), intravenous access was established with an 18 gauge intravenous cannula and the patients were pre-loaded with ringer lactate solution at a rate of 15 mL/kg body weight. They all received injection of Metoclopramide 10 mg intramuscularly and injection of Ranitidine 50mg intravenously 30 min before the operation. Urinary catheterization was done with Foley's catheter. Baseline systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), heart rate (HR), $SPO_{2,}$ and fetal HR were recorded.

The participants were divided into two groups for anesthesia. Group O received 4 mg of ondansetron intravenously, while Group P received 0.075 mg of palonosetron. SA was administered 5 min after drug administration, performed by a senior anesthesiologist. The procedure involved identifying bony landmarks, preparing the skin with povidone-iodine and spirit, and draping it sterilely. The L3-L4 and L2-L3 interspinous spaces were identified, and the skin was infiltrated with 1–2 mL of 2% lignocaine. A 25-27G Quienke spinal needle was inserted, and once the cerebrospinal fluid was obtained, 11 mg of bupivacaine was injected. The site was then dressed antiseptically.

After SA, the patient was placed supine with a wedge under the right hip and given oxygen. Surgery commenced once a T6-level sensory block was achieved. Vital parameters were monitored regularly.

In cases of hypotension or bradycardia, 100 mcg of phenylephrine or 0.6mg of atropine was administered, respectively. Oxytocin and fentanyl were given as needed, and dexamethasone was used for nausea and vomiting. Data collected included age, body mass indexes (BMI), ASA PS status, baseline and intraoperative vital signs, episodes of hypotension and bradycardia, vasopressor and atropine use, neonatal Apgar scores, and the incidence of post-operative nausea, vomiting, and shivering.

The statistical analysis utilized SPSS version 21.0, presenting quantitative data as mean and standard deviation (SD), while qualitative data were summarized using frequency and percentage tables. Unpaired t-tests were employed for quantitative data, and Chi-square tests were used for qualitative data. $p<0.05$ was taken as statistically significant.

Inclusion criteria

The following criteria were included in the study:

1. Patients undergoing lower segment cesarean section under SA
2. Age 18–35 years
3. Those who gave informed and written consent to be part of the study
4. ASA II patients.

Exclusion criteria

The following criteria were excluded from the study:

1. Those who refused consent
2. Age below 18 and above 35 years
3. ASA III or above
4. Patients with contraindications to SA, allergy to ondansetron and palonosetron, or local anesthetics
5. History of hypertension, coronary artery disease, or other cardiovascular diseases.

RESULTS

The mean age for Group O was found to be 26.62±2.67, whereas the mean age of patients in Group P was found to be 26.86±4.58. The difference in mean age of the studied groups showed that the mean age was comparable in both groups with no statistically significant difference (p=0.674) (Table 1).

In the presented table, the mean BMI for Group O was found to be 25.42 with a SD of ±1.42, whereas for Group P, the mean BMI was reported as 26.24 with an SD of ±1.90. The comparison of the mean BMI values between these two groups indicated that they were relatively similar, with no statistically significant difference noted (0.3583) (Table 2).

In our study, all patients belonged to the ASA II category because ASA II was the inclusion criteria of the study. HRs of Group O and Group P were monitored over various time intervals (0–45 min), and both groups displayed slight variations in HR across the measured time points. However, none of these differences reached statistical significance, as indicated by p-values consistently above the threshold for significance ($p<0.05$). This suggests that, overall, the HR patterns between Group O and Group P were comparable throughout the observation period without any significant deviations. The values exhibited minor differences in mean SBP between the groups for each measurement. Most of these differences were not statistically significant. Notably, only one measurement shows a statistically significant difference with a *p*-value of 0.032 (at 18 min). In all other instances, the *p*-values range from 0.051 to 0.967, indicating no significant difference in SBP between the groups. The mean DBP values of both groups show minor fluctuations over time. However,

Table 1: Comparison of mean age of the studied cases

Age Group	Group O		Group P		p-value
	Mean	SD	Mean	SD	O versus P
Age (in years)	26.62	2.67	26.86	4.58	0.674

SD: Standard deviation

Table 2: Comparison of body mass index of the studied cases

Body Mass Index	Group				
	Group O		Group P		p-value
	Mean	SD	Mean	SD	O versus P
BMI (kg/sq. m)	25.42	1.42	26.24	1.90	0.3583

most of these differences were not statistically significant. Notably, at the 15-min (p=0.021) and 21-min (p=0.042) marks, there was a significant difference in DBP (Table 3).

In Group O, when the mean MAP values were compared with the baseline values, there were significant differences at 3, 6, and 9 min. In Group P, there was a significant difference in mean MAP values at 3 min, 6 min, 9 min, 12 min, 15 min, 18 min, 21 min, 24 min, 27 min, and 30 min with the baseline values. At each time point, in patients in both the groups, no clinically defined hypotension was found (Fig. 1).

The comparison of mean SPO2 levels at different times showed that in both the groups, SPO2 was maintained and there was no significant difference in SPO2 levels of both the groups at various points (P>0.05) (Fig. 2).

Average phenylephrine in microgram (mcg) was comparable between the two groups and there was no statistically significant difference (Table 4).

Table 3: Comparison of heart rate, systolic blood pressure, and diastolic blood pressure at various time intervals

Haemodynamic Parameters	Group O		Group P		p-value
	Mean	SD	Mean	SD	O versus P
Mean Heart Rate					
0 min	90.67	11.70	87.05	11.31	0.148
3 min	92.43	12.78	89.50	11.44	0.237
6 min	91.95	12.28	91.10	11.68	0.703
9 min	92.48	12.67	91.48	11.36	0.658
12 min	93.71	11.80	92.88	11.84	0.664
15 min	93.19	11.78	93.62	11.59	0.97
18 min	93.24	12.37	95.24	12.36	0.612
21 min	94.36	12.29	95.40	11.66	0.868
24 min	94.00	12.49	96.69	11.39	0.419
27 min	94.52	12.79	95.76	10.65	0.738
30 min	93.31	11.29	96.79	11.67	0.238
35 min	93.81	11.98	96.67	9.95	0.334
40 min	94.10	12.24	97.21	9.70	0.273
45 min	94.76	11.50	97.95	10.61	0.243
Systolic blood pressure					
0 min	122.57	6.93	121.29	6.34	0.125
3 min	116.43	9.40	116.07	9.40	0.967
6 min	116.69	8.76	115.69	10.31	0.428
9 min	118.69	6.76	117.81	8.43	0.463
12 min	120.31	7.22	117.69	7.42	0.069
15 min	120.55	6.87	119.60	5.53	0.347
18 min	121.10	6.12	118.21	7.09	0.032
21 min	121.10	6.19	119.00	5.71	0.086
24 min	121.79	6.88	119.36	6.47	0.079
27 min	120.33	8.82	118.38	6.67	0.239
30 min	120.90	8.82	118.12	7.22	0.051
35 min	120.64	5.86	118.10	7.27	0.06
40 min	121.55	6.12	120.10	5.44	0.194
45 min	121.71	6.12	119.57	5.84	0.086
Diastolic Blood Pressure					
0 min	77.02	6.98	76.33	6.11	0.606
3 min	72.24	9.27	71.83	7.85	0.949
6 min	73.19	7.99	71.52	7.64	0.201
9 min	73.74	7.43	72.83	6.31	0.394
12 min	74.24	5.49	72.45	5.84	0.089
15 min	75.24	5.55	72.67	5.06	0.021
18 min	75.10	5.72	73.19	6.00	0.079
21 min	75.55	4.67	73.52	5.01	0.042
24 min	74.62	5.53	73.05	5.52	0.078
27 min	76.14	9.48	73.24	5.35	0.068
30 min	75.24	4.90	73.29	5.32	0.057
35 min	76.33	5.76	75.38	4.46	0.359
40 min	76.81	5.09	75.17	4.95	0.129
45 min	77.45	5.73	76.07	5.14	0.211

Incidence of hypotension was comparable between the two groups and there was no statistically significant difference. Sedation scores were comparable between the two groups. There was no incidence of bradycardia in any patients in any of the groups.

The neonatal outcome was assessed by APGAR score. An APGAR score of <7 was taken as suggestive of birth asphyxia. The analysis of newborns in both groups showed that the mean APGAR scores were comparable in both groups with no statistically significant difference (p>0.05) (Fig. 3).

DISCUSSION

Ondansetron was used to attenuate arterial blood pressure drop due to spinal anesthesia in general surgery cases by Owczuk *et al*. [14] and in obstetric population by Sahoo *et al*. [15], Ortiz–Gómez *et al*. [16]. Previously, palonosetron was used in a study to see its effects on PONV in patients undergoing gynecological surgeries under spinal anesthesia. In that study, conducted by Narayeneppe *et al*. [17], the incidence of hypotension was 30%. In our study, we compared the effects of palonosetron and ondansetron to attenuate hypotension in obstetric patients undergoing elective cesarean section under spinal anesthesia.

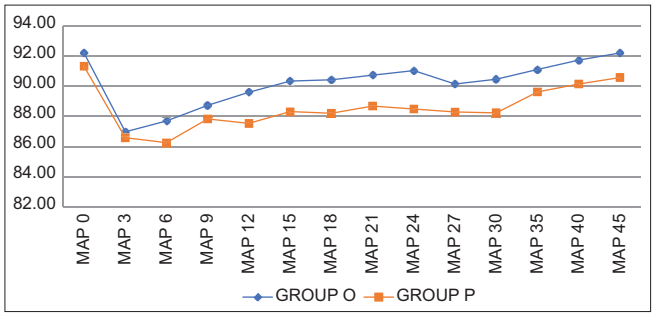

Fig. 1: Comparison of mean arterial pressure in both groups at various time intervals

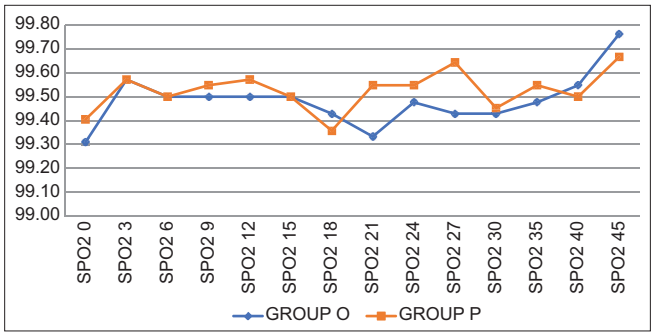

Fig. 2: Comparison of mean SPO_2 in both the groups at various time intervals

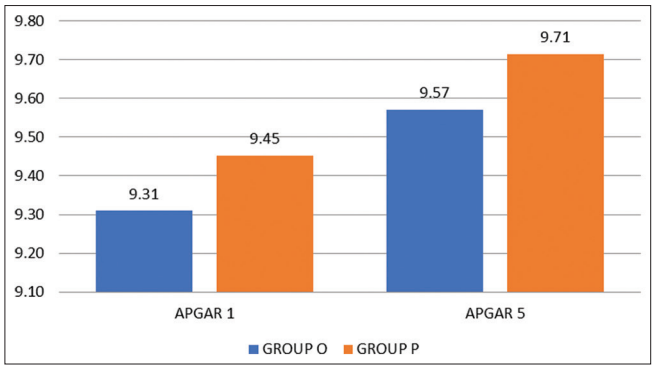

Fig. 3: Comparison of APGAR score in both the groups

Table 4: Comparison of average phenylephrine use in both groups

Vasopressor	Group				
	Group O		Group P		p-value
	Mean	SD	Mean	SD	O versus P
Average phenylephrine use (mcg)	30.95	46.79	30.95	51.74	1

Owczuk *et al*. [14] and Ortiz-Gómez *et al*. [16] used ondansetron 8mg in their studies. Whereas Sahoo *et al*. [15] used ondansetron 4 mg in their studies. We used ondansetron 4mg in our study. The anesthetic technique used by different investigators might influence and account for the difference in the results of their studies. We used 11mg of hyperbaric bupivacaine, where Sahoo *et al*. [15] used 10 mg and Owczuk *et al*. [14] used 20 mg, Ortiz-Gómez *et al*. [16] used doses after personalized for each dose (height in cm × 0.06) along with fentanyl. Trabelsi *et al*. used 10 mg of hyperbaric bupivacaine with 2.5 mcg of injection Sufentanyl [18].

The definition of hypotension also differs in different studies. Owczuk *et al*. [14] did not present any definition, while Ortiz-Gómez *et al*. [16] defined hypotension <75% of the baseline SBP value. Sahoo *et al*. [15] defined hypotension when SBP<90 mm of Hg or DBP <60 mm of Hg. Trabelsi *et al*. [18] defined hypotension as a decrease from baseline value ≥20% in SBP, which we took as a parameter in our study. Sahoo *et al*. [15] used intravenous fentanyl to treat intra-operative pain and tramadol or promethazine to treat adverse effects. These two drugs could modify hemodynamics during the study period. In our study, we excluded the patients as a study case due to inadequate analgesia.

In our study, we preloaded the patients with Ringer lactate solution (15 mL/kg) before spinal anesthesia. Whereas Trabelsi *et al*. [18] used a fast infusion of normal saline(10 mL/kg) 5 min before spinal anesthesia. Owczuk *et al*. [14] used no preloading or coloading during the study period and Ortiz-Gómez *et al*. [16] coloaded their study subjects with colloid (8 mL/kg).

As we know, oxytocin protocol after umbilical cord clamping might influence maternal hemodynamics, we used 10 IU of oxytocin dissolved in 500 mL of intravenous fluid slowly. Sahoo *et al*. [15] and Trabelsi *et al*. [18] did not mention such oxytocin protocol. Ortiz-Gómez *et al*. [16] used low doses of oxytocin (1IU) followed by an infusion of oxytocin @2.5IU/h. Thus, it had been seen that studies differ in types of loading fluids, types of vasopressors used, and oxytocin protocol. We used phenylephrine to treat hypotension as the standard of care (no fetal acidosis).

Sahoo *et al*. [15] found that 4 mg of ondansetron could attenuate hypotension in obstetric patients receiving spinal anesthesia, but Ortiz-Gómez *et al*. [16] found that it did not influence the incidence of maternal hypotension though reducing the severity and frequency of hypotension. Owczuk *et al*. [14] found in their study that MAP and SBP values were significantly higher in the ondansetron group with no significant difference in DBP and HR values. Trabelsi *et al*. [18] found in their study that SBP, DBP, and MAP values were higher in the ondansetron group than control group in the 4^{th} and 10^{th} min and no difference thereafter. The incidence of hypotension in the ondansetron group was 37.5%. Narayeneppe *et al*. [17] found in their study that palonosetron also reduced the incidence of hypotension in an obstetric population (30%). In our study, both ondansetron and palonosetron equally reduced the incidence of hypotension in an obstetric population (30.95% in both). Vasopressor consumption was also comparable in both groups. None of the drugs showed any significant adverse effects during the study period. Similar findings were also reported by authors such as Sharma *et al*. [19] and Campos *et al*. [20].

CONCLUSION

Our study showed that prophylactic ondansetron, as well as palonosetron, were equally effective in reducing the incidence and severity of hypotension in healthy parturients following spinal anesthesia with hyperbaric bupivacaine for elective LSCS.

CONFLICT OF INTEREST

None

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