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Research Article

Randomized double blind comparative study of the efficacy of ondansetron and palonosetron in prevention of postoperative shivering in patients undergoing elective LSCS under spinal anaesthesia

Authors
Dr Rumani Ruku[1*], Dr Nikita Gandotra[2]
[1]Department of Anaesthesiology and Intensive Care
[2]Department of Obstetrics and Gynaecology, SMGS Hospital, Jammu
*Corresponding Author
Dr Rumani Ruku
Department of Anaesthesiology and Intensive Care

Abstract

Background: *Post anesthesia shivering (PAS) is a common, distressing experience. Ondansetron, the classical 5-HT3 antagonist has been in use for its prevention since long. Palonosetron, a newly introduced potent antiemetic drug with better pharmacodynamics. A study was conducted to compare the efficacy of ondansetron and palonosetron in preventing PAS in patients undergoing elective lower segment caesarean section (LSCS) under spinal anaesthesia. Different observations suggest that the serotonergic system has a role in the control of postanesthetic shivering. Therefore, the sudy compared the effect of ondansetron and palonosetron in preventing PAS in patients undergoing elective lower segment caesarean section (LSCS) under spinal anaesthesia.*

Methods: *A double blind randomized prospective study was conducted in the Department of Anesthesia, GMC Jammu. A total of 64 patients scheduled for elective LSCS under spinal anesthesia were randomly allocated to one of the two study groups. Accordingly, 8 mg of ondansetron or 0.075 mg palonosetron was administered in the same volume intravenously 30 min preoperatively.*

Results: *No statistically significant intergroup difference was observed in the duration of surgery, and nasopharyngeal temperature. However, statistically significant difference was recorded for PAS, with 28.12% patients (9/32 patients) experienced shivering in Group I at 30-Minute interval, which was significantly lower in Group II (18.75%; 6 out of 32 patients) and p-value was 0.012. The difference was significant at 60-Minutes interval (p = 0.044) also.*

Conclusion: *When used prophylactically, palonosetron significantly reduced incidence of PAS compared to ondansetron. However, further studies with larger sample size and more heterogeneous groups are suggested.*

Keywords: *Spinal anesthesia, Lower Segment Caesarean Section, Ondansetron, palonosetron, post-anesthesia shivering, Core Temperature.*

Introduction

In human beings, the core temperature is normally maintained within 36.5- 37.5 degree Celsius, even in presence of an adverse environmental temperature, by a combination of behavioral and physiological response.[1] Any reduction in core body temperature may lead to shivering which is a bodily mechanism to increase the body temperature. The occurrence of shivering during and after anesthesia is well recognized since long and described by various terms. Shivering-like tremor in volunteers given neural-axial anesthesia is always preceded by core hypothermia and vasoconstriction above the level of the block.[2] Post anesthesia shivering produces undesirable physiological consequences such as raised oxygen consumption & hypoxemia, increased cardiac work, lactic acidosis and lower mixed venous oxygen saturation, it also hinders postoperative recovery.[3] It can cause arterial hypoxia and has been shown to correlate with increased risk of myocardial ischemia. Shivering, however, is not an uncommon complication of spinal and general anesthesia, being reported with an incidence of 40–60% in various studies.[4,5] Perioperative hypothermia and shivering is usually prevented by physical methods, and a wide range of drugs like: pethidine, fentanyl, alfentanil, sufentanil, tramadol, buprenorphine, doxapram, clonidine & ketanserin etc, have been reported to be effective in suppressing shivering.[6,7] Besides, Endogenous peptides, biogenic monoamines, cholinemimetic drugs, and possibly N-Methyl-D-aspartic acid (NMDA) antagonists seem to help in modulation of central thermoregulatory control mechanisms. Different patterns of shivering has been noted in different forms of anesthesia. Besides, age, type of surgery, duration of surgery, baseline body core temperature, and associated comorbidities independently influence triggering of shivering and its severity as well.[4,5,8,9]

Various opioid and non opioid drugs, often used in the prevention and management of postoperative shivering, are associated with potential side effects, including hypotension, hypertension, sedation, respiratory depression, nausea and vomiting. More recently, 5-HT3 receptor antagonists have emerged as a means of preventing peri- and postoperative shivering, but, their efficacy is yet to be proven.[10] Ondansetron is a specific 5HT3 antagonist that may affect thermoregulation & PAS. Recently it has also been tried successfully for prevention of shivering in dose of 8mg I/V without any side effects.[11]

As there are very few studies in relation to use of ondansetron and palonosetron in prevention of postoperative shivering during spinal anaesthesia and there are even fewer comparative studies specifically evaluating use of low dose ondansetron and palonosetron for prevention of shivering during spinal anaesthesia. So the present double-blind prospective study was conducted to evaluate and compare the relative efficacy of the two drugs, for specific outcomes of incidence of shivering (PAS) and severity of shivering.

Material and Methods

A double blind randomized prospective study was conducted in the Department of Anesthesia, GMC Jammu. This study was carried out over a period of 6 months. 64 female patients, of age group 18 - 38 years, were enrolled and randomly assigned to the two study groups of 32 each. Group A (n=32) received Ondansetron 8 mg I/V and Group B (n=32) received 0.075 mg of Palonosetron I/V in the same volume intravenously 30 min preoperatively. Patients were randomly divided in a double-blind manner into two equal groups of 32 patients each according to computer generated random number table. Group allocation was done by an anesthesiologist who was not aware of the study protocol. Nasopharyngeal temperature was recorded every 10 minutes from baseline to recovery. All patients were observed for 90 min postspinal for PAS. After recovery from anaesthesia the occurrence of shivering was documented clinically by an observer who was unaware of the group assignment.

Inclusion Criteria: Patients in the age group of 18 to 38 years with singleton pregnancy belonging

to American Society of Anaesthesiologists (ASA) grade I and II undergoing elective lower segment cesarean section (LSCS) under spinal anesthesia were included in the study.

Exclusion Criteria: Patients with allergy to 5-HT3 receptor antagonist drugs, age <18 years or >38 years, psychological disorders, those with initial body temperature >38 ºC or <36 ºC, those requiring sedation/supplementation with other anesthetic drugs, or blood transfusion during period of observation were excluded from the study.

Patients were kept empty stomach for 8 hours as per standard protocol pre-operatively. Ranitidine in the dose of 50 mg and metoclopramide in the dose of 10 mg were administered intravenously prior to sending the patient to the operating room.

In the operating room, patients were given either 8 mg of ondansetron or 0.075 mg of palonosetron i/v, 30 minutes prior to spinal anesthesia as per their assigned group. Both the drugs were made to 4 ml volume in 5 ml syringes. Subarachnoid block was established using 2.6 ml of 0.5% bupivacaine (heavy) and block adequacy was ensured.

Intraoperatively, all patients were covered in surgical drapes and the ambient temperature in the OT suite was maintained between 22 and 24 ºC. Supplemental oxygen administered at a rate of 3-4 L/min through face mask. All intravenous fluids were at room temperature prior to administration. On arrival in the operating room, a peripheral I/V access with venous cannula of 18/20 G was achieved. Monitors recording ECG (HR), Blood pressure (NIBP), SpO2 & Respiratory rate were attached. All patients were coloaded with 500 ml of Ringer lactate solution while establishing spinal anesthesia and no anesthetic supplementation was done intraoperatively. Nasopharyngeal temperature was measured prior to the beginning of surgery and then recorded at every 10 min interval for next 90 min. Perioperatively, bradycardia, hypotension, and vomiting were also monitored and treated with atropine, mephenteramine and metoclopramide respectively in appropriate doses.

Shivering was defined as readily detectable fasciculations or tremors of face, trunk or limbs of a minimum of 15-seconds duration. During the surgery, shivering score was recorded at 10 minute interval. Incidence of shivering both in case of Ondansetron and Palonosetron was studied as the primary outcome, while severity of shivering was graded based upon study by Wrench *et al*.(7)(Table:1). All patients were observed for 90 min postoperatively and PAS was documented by visual score. Patients with Grade 3 or 4 of shivering were included for the study. Severe PAS was treated with 0.5 mg/kg boluses of tramadol I/V.

Based on the previous studies, incidence of post-spinal shivering in ondansetron and palonosetron was assumed to be 40% and 15% respectively. Taking power of the test to be 90%, sample size of 63, was calculated vide two-tailed null hypotheses.

Due approval was obtained from Institutional Ethical Committee. Results obtained were analyzed using MS Excel Software. Results were presented as mean ± standard deviation (SD) and number (and %). Chi-square test was applied for categorical variables between the two groups. *P* value of <0.05 was considered as statistically significant.

Table 1: Grading of shivering

Grade	Features
Grade 0	No shivering
Grade 1	One or more of the following: Peripheral vasoconstriction, pilo-erection, and peripheral cyanosis without other cause, but without visible muscle activity.
Grade 2	Muscular activity in only one muscle group
Grade 3	Muscular activity in more than one muscle group but not generalized
Grade 4	Shivering involving the whole body

Results

Mean of the age, weight, height, duration of surgeries and nasopharyngeal temperature was calculated in both the groups. No significant intergroup difference was observed in demographic variables (age, height and weight), duration of surgery, and nasopharyngeal temperatures. (Table 2)

Table 2: Demographic / baseline characteristics

Variables	Group I (*n* = 32)	Group II (*n* = 32)	*P-value*
Age	29.44 ± 4.23	28.5 ± 3.67	0.392
Weight in Kg	69.28 ± 6.52	68.46 ± 6.05	0.661
Height in Cms	165.4 ± 4.6	166.1 ± 4.8	0.705
ASA Class (I/II)	22/10	21/11	0.186
Duration of surgery, in minutes	53.4 ± 9.5	51.7 ± 8.2	0.338
Nasopharyngeal Temperature	96.3 ± 0.5	95.8 ± 0.7	0.329

Values are represented as mean ± SD.

28.12% patients (9 out of 32 patients) experienced shivering in Group I at 30-Minute interval, which was significantly lower in Group II (18.75%; 6 out of 32 patients) and *p*-value was 0.012. Similarly, the difference was significant at 60-Minutes interval (p = 0.044) also and not significant at 90-Minute interval. (Table 3)

Table 3: Incidence of shivering

Incidence of Shivering		Group I (*n* = 32)	Group II (*n* = 32)	*P-value*
At 30 Minutes	Grade 0	23 (71.88%)	26 (81.25%)	0.012*
	Grade 3	9 (28.12%)	6 (18.75%)	
At 60 Minutes	Grade 0	27 (84.38%)	30 (93.75%)	0.044*
	Grade 3	5 (15.62%)	2 (6.25%)	
At 90 Minutes	Grade 0	31 (96.88%)	32 (100%)	0.879
	Grade 3	1 (3.12%)	0 (0 %)	

*p<0.05 = significant

Mean blood pressure and heart rate were recorded intra-operatively at various time intervals and were comparable in all the groups. Ondansetron did not alter the hemodynamic profile of either group intra-operatively.

Table 4: Heart Rate at different time intervals

Time Interval (minutes)	Group A	Group B
Baseline (Before GA)	82.8 ± 5.7	84.3 ± 6.9
10	80.2 ± 6.6	81.7 ± 5.5
20	78.9 ± 7.0	77.6 ± 6.2
30	76.7 ± 5.9	76.7 ± 6.3
40	75.0 ± 5.6	75.4 ± 4.8
50	72.4 ± 4.6	72.1 ± 3.5
60	72.4 ± 4.0	72.3 ± 4.1
70	72.2 ± 4.3	73.3 ± 3.6
80	73.6 ± 3.5	74.7 ± 4.5
90	75.0 ± 3.9	74.3 ± 2.0

Values are represented as mean ± SD.

There was no statistically significant difference in the Mean Core Temperature at various time intervals in between the two groups, although there was decrease from baseline to the end of surgery. (Figure 1)

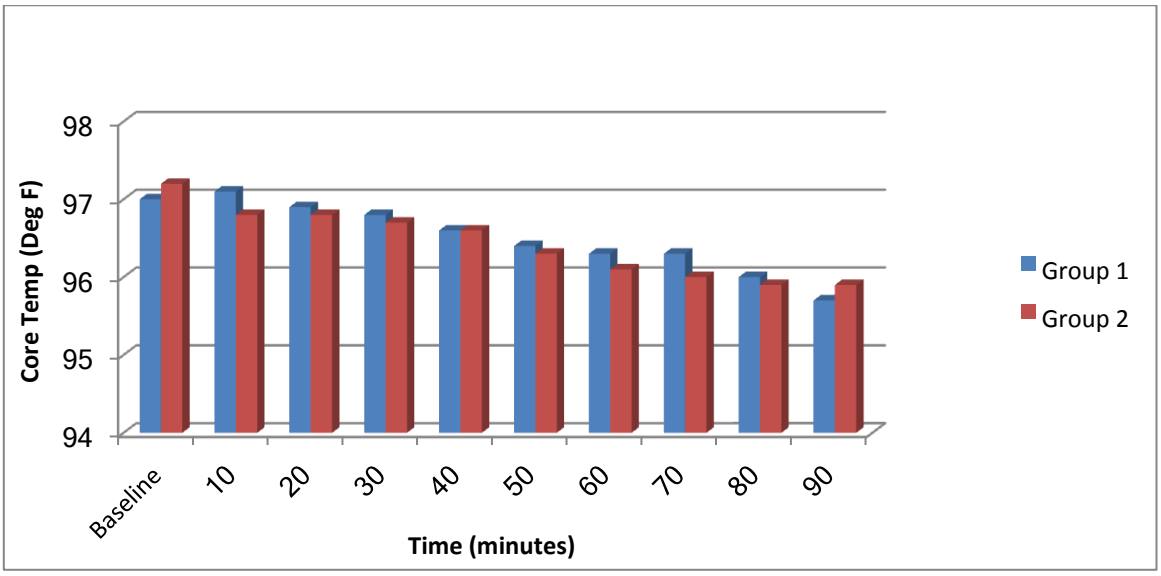

Figure 1: Mean Core Temperatures at various time intervals

Discussion

Post anesthesia shivering (PAS) is a commonly encountered complication with general as well as spinal anesthesia. Multiple pharmaco-therapeutic agents have been studied for prevention of PAS which include various classes of drugs, e.g., alpha-2 agonists, opioids, benzodiazepines, choline-mimetics, NMDA antagonists, and several other drugs such as magnesium sulfate and lignocaine.[4,8] Various observations suggest that the serotonergic system has a role in the control of post anesthesia shivering. It has been shown that a 5-Hydroxytryptamine-3 (5-HT3) antagonist, Ondansetron has anti-shivering effect. Given the variety of neurotransmitter systems known to be also involved in regulating shivering, an inhibitory effect at the 5HT3 receptor probably results from a generalized thermoregulatory inhibition, related to the inhibition of serotonin uptake on the preoptic anterior hypothalamic region, where the bulk of thermoregulatory control occurs.[12]

5-HT3 antagonists have demonstrated definite beneficial role in prevention of PAS and have an established favorable clinical profile and less side effects, such as dizziness, hypotension, etc., Ondansetron is notable for its lack of hemodynamic side effects.

Palonosetron is a 5-HT3 receptor antagonist, newly introduced as a potent, single stereo-isomeric compound, with a fused tricyclic ring system structure attached to a quinuclidine moiety in contrast to first-generation drugs, which are based on a three substituted in dole structure. The binding affinity of palonosetron to 5-HT3 receptor is also 30 times higher than the older 5-HT3 receptor antagonists.[13-15] Owing to its different chemical structure, long plasma half-life and receptor affinity, palonosetron is presumed to interact efficiently at molecular level with 5-HT3 receptors at sites different from or in addition to that of ondansetron and granisetron binding.[13]

Both ondansetron and palonosetron have been widely studied separately, but their comparative study for efficacy on PAS after subarachnoid block, is less studied. Palonosetron has not yet been studied much for its efficacy on PAS after neuraxial blocks. Existing data on effect of palonosetron on PAS after spinal anesthesia are scarce. Jo *et al.*[14] demonstrated the incidence of PAS to be 21% in their study with prophylactic use of 0.075 mg palonosetron intravenously, which was 18.75% in our study. However, Jo et al.14 conducted the study in laparoscopic cholecystectomy with general anesthesia in patients of age group 65-80 years, which might explain even higher incidence of PAS compared to our study.[14]

Lakhe *et al.*[16] found an incidence of PAS of around 16.7% (5 out of 30 patients) with 4 mg prophylactic intravenous ondansetron in surgeries

being performed under spinal anesthesia. In the present study, incidence of shivering was noted to be lower in Group II (palonosetron group) than Group I (ondansetron group) with comparatively higher incidence of PAS 28.12% in patients receiving Ondansetron. Since our study was conducted exclusively in pregnant ladies with peculiar hemodynamic milieu undergoing LSCS, it probably might have contributed to a comparatively higher rate of PAS.

In a study conducted by Badawy et al.[17] on obstetric patients, undergoing elective LSCS under spinal anesthesia, 51% incidence of PAS was observed in control group (with normal saline) and 26% with 8 mg intravenous ondansetron. Incidence of shivering in our study after administration of prophylactic ondansetron was observed to be 28.12% at 30 minutes, which was comparable. Similarly, the difference was significant at 60-Minutes interval (p = 0.044) also and not significant at 90-Minute interval.

During the study, hemodynamic parameters like heart rate, systolic BP, diastolic BP and mean arterial pressure were monitored every 10 minutes throughout intra-operative period. There has not been much difference among the two groups in relation to hemodynamic parameters.

In our study, nasopharyngeal temperature was measured, using non-invasive nasopharyngeal temperature probe. Nasopharyngeal temperature is one of the reliable sites for measurement of core temperature. The mean nasopharyngeal temperature decreased significantly after spinal anaesthesia in both the groups with respect to baseline values. This is expected because hypothermia occurs during spinal anaesthesia due to internal redistribution of body heat, heat loss to the environment and inhibition of centrally mediated thermoregulatory control.

A limitation of the study is that the study was done only in elective LSCS surgeries under spinal anesthesia; hence, extrapolation of the results to other major surgeries, under general anesthesia, or on the male population, needs further studies for generalization. Small sample size was another limitation in our study.

Conclusion

Palonosetron (0.075 mg) was found significantly more effective than ondansetron (8mg) during spinal anesthesia in preventing PAS. However, further studies with larger sample size need to be undertaken to establish and generalize the beneficial effects of palonosetron on postspinal shivering among other major surgeries.

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