Original Article

Efficacy of ondansetron and palonosetron in prevention of shivering under spinal anesthesia: A prospective randomized double-blind study in patients undergoing elective LSCS

Manoj K Sharma, Deepak Mishra, Nitin Goel

Department of Anaesthesiology and Critical Care, Military Hospital, Meerut, Uttar Pradesh, India

Abstract

Background and Aims: Postanesthesia shivering (PAS) is a common, distressing experience. Ondansetron, the classical $5HT_3$ antagonist has been in use for its prevention since long. Palonosetron, a newly introduced potent antiemetic drug with better pharmacodynamics is currently in use by clinicians. Hence, 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.

Material and Methods: A total of 84 patients scheduled for elective LSCS under spinal anesthesia were randomly allocated to one of the two study groups (Group O & P). Accordingly, 8 mg of ondansetron or 0.075 mg palonosetron was administered in the same volume intravenously 30 min preoperatively. Sublingual temperature was recorded regularly. All patients were observed for 90 min postspinal for PAS. Observations were analyzed statiscally.

Results: No statistically significant intergroup difference was observed in the duration of surgery, and sublingual temperature. However, statistically significant difference was recorded for PAS (23.8% in ondansetron group, 9.5% in palonosetron group).

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

Keywords: LSCS, ondansetron, palonosetron, postanesthesia shivering, spinal-anesthesia

Introduction

Shivering is not only a leading cause of discomfort to patients in perioperative period, but also hinders postoperative recovery significantly. Shivering in perioperative period causes many folds increase in metabolism, oxygen demand, and consumption besides CO_2 production at cellular level. In severe cases, resultant lactic acidosis and hypoxemia may adversely affect peri- and postoperative outcome. Shivering is not an uncommon complication of spinal and general anesthesia, being reported with an incidence of 40–60% in various studies.[1,2]

Shivering is termed as an involuntary and repetitive skeletal muscles activity.[1] It occurs as a response to hypothermia in majority of cases; however, it is also reported in normothermic patients. Mechanisms mediated through uninhibited spinal reflexes, postoperative pain, and hyperactive sympathetic activities been hypothesized. Different frequencies and

Address for correspondence:
Dr. Manoj K Sharma,
Department of Anaesthesiology and Critical Care, Military Hospital, Meerut, Uttar Pradesh - 250 001, India.
E-mail: manoj.congo@gmail.com

Access this article online

Quick Response Code:

Website: www.joacp.org

DOI: 10.4103/joacp.JOACP_215_18

How to cite this article: Sharma MK, Mishra D, Goel N. Efficacy of ondansetron and palonosetron in prevention of shivering under spinal anesthesia: A prospective randomized double-blind study in patients undergoing elective LSCS. J Anaesthesiol Clin Pharmacol 2021;37:63-6.

Submitted: 13-Jul-2018 **Revised:** 25-Jun-2019
Accepted: 27-Aug-2019 **Published:** 10-Apr-2021

patterns of shivering has been noted in different forms of anesthesia.[1]

Endogenous peptides, biogenic monoamines, choline-mimetic drugs, and possibly N-Methyl-D-aspartic acid(NMDA) antagonists seem to participate in integration and modulation of central thermoregulatory control mechanisms.[1-3] 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]

A plethora of opioid and non opioid drugs are often used in prevention and management of postoperative shivering, but 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. However, their efficacy is yet to be proven conclusively.[5,6]

A double-blind prospective study was conducted to assess and compare the newly available 5-HT3 receptor antagonist "Palonosetron" against the older drug of same class "Ondansetron" in preventing PAS among patients undergoing spinal anesthesia.

Material and Methods

After obtaining ethics committee approval this, study was carried out over a period of 10 months from Jul 17 to Apr 18. In this study, using computer software 84 patients were enrolled and randomly assigned to the two study groups (Group" O", the Ondansetron group and Group" P", the Palonosetron group).

Patients in the age group of 18-35 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. Patients with allergy to 5-HT3 receptor antagonist drugs, psychological disorders, 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.All patients were assessed for anesthesia/surgery fitness in preanesthetic clinic as per protocol and inclusion criteria. Patients were kept nil orally for solids 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 (i/v) prior to sending the patient to 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 and the operation theater (OT) staff who prepared the drugs was kept unaware of the study. Subarachnoid block was established using 2.8 ml of 0.5% bupivacaine (heavy) with 25/26G Quincke needle and block adequacy was ensured.

Preoperatively, all patients wore a cotton gown and were covered by a single blanket. Intraoperatively, all patients were covered in surgical drapes and were not actively warmed. However, the ambient temperature in the OT suite was maintained between 22 and 24 ºC and supplemental oxygen administered at a rate of 3-4 L/min through face mask. All intravenous fluids were at room temperature prior to administration. All patients were coloaded with 500 mL of Ringer lactate solution while establishing spinal anesthesia and no anesthetic supplementation was done intraoperatively. SpO_2, electrocardiograph (ECG), and non-invasive blood pressure (NIBP) were monitored as per ASA standards. Sublingual temperature was measured prior to the beginning of surgery and then recorded at every 30 min interval for next 90 min. Perioperatively, bradycardia, hypotension, and vomiting were monitored and treated with atropine, mephenteramine and metoclopramide respectively in appropriate doses. Severe PAS was treated with 5 mg boluses of pethidine i/v titrated to effect as and when required. Grading of shivering was adapted from the study by Wrench *et al.*[7] [Table: 1] All patients were observed for 90 min postoperatively and patients with grade 3 or 4 of shivering were included for the study.

Randomization was done using computer software (MS-Excel) which assigned numbers to each case. Odd numbered patients were given ondansetron and named Group "O" and even numbered patients were given palonosetron and named Group "P". Since it was a double-blind study the anesthesiologist administering the drug, the patient and the technician who observed the patient for shivering were kept unaware of the content of the syringe.

Medical calculator from medicalc.org was used for sample size calculation for testing two-tailed null hypotheses. Based

Table 1: Grading of shivering (adapted from Wrench *et al.*)[8]

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	Visible muscle activity confined to one muscle group
Grade 3	Visible muscle activity in more than one muscle group
Grade 4	Gross muscle activity involving the whole body

on the previous studies, incidence of postspinal shivering in ondansetron and palonosetron was assumed to be 40% and 15% respectively. A total of 42 patients (n = 42) in each group participated in the study. Observations obtained were analyzed using the Statistical Package for the Social Sciences (SPSS). Results are presented as mean ± standard deviation (SD) and number (%). Chi-square/Fisher's exact test was applied for categorical variables between the two groups. A P value of <0.1 was considered as statistically significant.

Results

The present study enrolled 42 patients in each study group (Group "O" and Group "P"). Patient characteristics are described in Table 2. Mean of the age, height, weight, duration of surgeries, and sublingual temperature was calculated in both the groups, as some of them are independent risk factors for development of postspinal shivering and others determine the extent of distribution of drug in subarachnoid space. No significant intergroup difference was observed in demographic variables (age, height, and weight), duration of surgery, and sublingual temperatures. Major indication in both the study groups was post-LSCS pregnancy; however, few other indications included in the study have been noted in Table 3.

Although 23.8% patients (10 out of 42 patients) experienced shivering in "O" group, it was significantly lower in "P" group (9.5%; 4 out of 42 patients) and P value was 0.07, which in our study was deemed statistically significant.

Table 2: Baseline characteristics of study population

Variables	Group "O" (n=42)	Group "P" (n=42)	P
Age	28.1 (3.7)	28.5 (3.3)	0.336
Height	161.9 (4.1)	162.4 (4.5)	0.657
Weight	68.7 (7.6)	67.3 (8.9)	0.521
Duration	41.8 (8.1)	41.2 (7.1)	0.711
Sublingual Temperature	95.6 (1.0)	95.9 (0.8)	0.154

Values are represented as mean (SD)

Table 3: Indication of surgery

Indication for LSCS	Group "O" (n=42)	Group "P" (n=42)
Post-LSCS	31 (73)	38 (90.5)
Failed induction	4 (9.5)	2 (4.7)
Breech presentation	5 (11.9)	0
Gestational hypertension	1 (2.3)	2 (4.7)
IHCP	1 (2.3)	0

Values are represented as number (percentage)

Discussion

Peri- and postoperative shivering also referred to as postanesthesia 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.[1,3] PAS has various mechanisms and contributory factors both in hypothermic and normothermic patients. Redistribution of body heat from core to the peripheral compartment (secondary to sympathetic block and peripheral vasodilatation), loss of thermoregulatory vasoconstriction below the level of the spinal block, and alteration of thermoregulatory mechanism under central neuraxial block are some of the contributory mechanisms to this response. In addition, rapid administration of cold intravenous fluid also augments the development of shivering in such patients.[8]

5-HT_3 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., Besides their usefulness as antiemetics, their effectiveness in prevention of PAS is being widely explored. Ondansetron, granisetron, dolasetron, and tropisetron were introduced in 1990s and were found to be beneficial in nausea and vomiting induced by chemotherapy. Palonosetron is a 5-HT_3 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 indole structure. Palonosetron has plasma half-life of approximately 40 h, while first generation drugs have half-lives of 5–12 h. The binding affinity of palonosetron to 5-HT3 receptor is also 30 times higher than the older 5-HT_3 receptor antagonists.[9-11] Antagonists of 5-HT3 receptor inhibit the neurotransmission involved in thermoregulation in the hypothalamus. 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.[10] Various meta-analysis have found definite advantage of administration of 5HT_3 antagonists in lowering the incidence of PAS during general and spinal anesthesia.[11,12] Both ondansetron and palonosetron have been widely studied separately but literature is in paucity on their comparative study for efficacy on PAS after subarachnoid block. Lakhe *et al.*[13] 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 our study, incidence of shivering was noted to be slightly higher with similar dose of intravenous

ondansetron.Our study was conducted exclusively in pregnant ladies with peculiar hemodynamic milieu undergoing LSCS, which probably might have contributed to a higher rate of PAS. In another study by Badawy and Mokhtar[14] in 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 25%, which is comparable with the observation made in this study.

Palonosetron has not yet been extensively studied for its efficacy on PAS after neuraxial blocks. Jo *et al*.[10] demonstrated the incidence of PAS to be 21% in their study with prophylactic use of 0.075 mg palonosetron intravenously. However, their study was conducted in laparoscopic cholecystectomy surgery with general anesthesia in patients of age group 65-80 years, which might explain higher incidence of PAS compared to our study. Jo *et al*.[6] observed the incidence to be about 27% when they used prophylactic palonosetron in patients undergoing gynecological laparoscopic surgery with propofol-remifentanil total intravenous anesthesia. However, this increased incidence may again be attributed to general anesthesia with remifentanil which has been considered associated with PAS. Both these studies involved patients undergoing surgery under general anesthesia but have not found any beneficial effect of palonosetron on PAS. Independent risk factors for development of PAS (laparoscopic surgeries, total intravenous anesthesia, general anesthesia, and elderly patients) present in both the groups might have mitigated the effect of palonosetron. Our study was conducted in young patients undergoing similar surgery (elective LSCS) under neuraxial block, which might be one of the important reasons for relatively lower (10%) incidence of PAS with palonosetron. Existing data on effect of palonosetron on PAS after spinal anesthesia are scarce. However, beneficial effects of 5-HT_3receptor antagonists are apparently more obvious with neuraxial blocks.

A limitation of the study is that only shivering of grade-3 and above was included in this study which might have missed some patients who had milder form of PAS. Small sample size was another limitation in our study. The study was done only in elective LSCS surgeries under spinal anesthesia; hence, extrapolation of the results to other major surgeries under general anesthesia needs further studies for generalization.

Conclusion

Palonosetron is more effective than ondansetron in preventing PAS in patients undergoing surgery under spinal anesthesia. However, considering the small sample size and homogenous nature of surgery and anesthesia, the authors believe that 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.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. De Witte J, Sessler DI. Perioperative shivering: Physiology and pharmacology. Anaesthesiology 2002;96:467-84.
2. Kamal MM, Hussein NS. Prevention of post spinal shivering by using ketamine plus Midazolam in comparison with Neopam. Egypt Anaesth 2011;27:1-5.
3. Kranke P, Eberhart LH, Roewer N, Tamer MR. Pharmacological treatment of postoperative shivering: A quantitative systematic review of randomized controlled trials. Anesth Analg 2002;94:453-60.
4. Eberhart LH, Doderlein F, Eisenhardt G, Kranke P, Sessler DI, Torossian A, *et al*. Independent risk factors for postoperative shivering.Anesth Analg 2005;101:1849-57.
5. Browning RM, Fellingham WH, O'Loughlin EJ, Brown NA, Paech MJ. Prophylactic ondansetron does not prevent shivering or decrease shivering severity during cesarean delivery under combined spinal epidural anesthesia: A randomized trial. Reg Anesth Pain Med 2013;38:39-43.
6. Jo YY, Kwak HJ, Lee MG, Lim OK. Effect of palonosetron on postanesthetic shivering after propofol-remifentanil total intravenous anesthesia. J Anesth 2013;27:533-40.
7. Wrench IJ, Singh P, Dennis AR, Mahajan RP, Crossley AW. The minimum effective doses of pethedine and doxapram in the treatment of post anaesthetic shivering.Anaesthesia1977;52:32-6.
8. Reddy VS, Chiruvella S. Clonidine versus tramadol for post spinal shivering during caesarean section: A randomized double-blind clinical study. J Obstet Anaesth Crit Care 2011;1:26-9.
9. Shash E, AbdullaM. Palonosetron: An overview. Adv Oncol 2010;8:18-20.
10. Jo YY, Kim YB, Lee D, Chang YJ, Kwak HJ. Implications of palonosetron in elderly patients undergoing laparoscopic cholecystectomy with respect to its anti-shivering effect. Aging Clin Exp Res 2016;28:83-8.
11. Zhou C, Zhu Y, Liu Z, Ruan L. 5-HT3 receptor antagonists for the prevention of postoperative shivering: A meta-analysis. JIntMedRes 2016;44: 1174-81.
12. Tie HT, Su GZ, He K, Liang S-R, Yuan H-W, Mou J-H. Efficacy and safety of ondansetron in preventing post-anesthesia shivering: A meta-analysis of randomized controlled trials. BMC Anesthesiol 2014;14:12.
13. Lakhe G, Adhikari KM, Khatri K, Maharjan A, Bajracharya A, Khanal H. Prevention of shivering during spinal anaesthesia: Comparison between tramadol, ketamine and ondansetron. JNMA J Nepal Med Assoc. 2017;56:395-400.
14. Badawy AA, Mokhtar AM. The role of ondansetron in prevention of post-spinal shivering (PSS) in obstetric patients: A double-blind randomized controlled trial. Egypt J Anaesth 2017;33:29-33.