Original Article

Prevention of Postanesthetic Shivering under Subarachnoid Block for Cesarean Section: A Randomized, Controlled Study Comparing Tramadol Versus Ondansetron

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Abstract

Background: Shivering is a frequent undesirable event in patients undergoing cesarean delivery under spinal anesthesia. Postanesthetic shivering has a multitude of deleterious effects and different methods have been used to prevent it. We therefore compare the efficacy of ondansetron to that of tramadol in preventing postanesthetic shivering in women undergoing cesarean section under subarachnoid block. **Aim:** Comparison of the efficacy of ondansetron to that of tramadol in preventing postanesthetic shivering in women undergoing cesarean section under subarachnoid block. **Subject and Methods:** This is a prospective, double-blind, placebo-controlled, randomized study. The patients (n = 109) were randomly allocated to three groups according to the study drugs, namely tramadol 50 mg group (Group T), ondansetron 4 mg group (Group O), and saline 4 ml group (Group S) using envelope randomization. Statistical analyses were done using Statistical Package for Social Sciences 20.0. **Results:** A total of 100 patients completed the study (33 in Group S, 33 in Group T, and 34 in Group O). The three groups were comparable with respect to demographic characteristics. Shivering was observed in 16 (48.5%) of the patients in Group S; 13 (39.4%) patients in Group T, and in only 2 (5.9%) patients in Group O. The differences in incidence of shivering were statistically significant between Groups O and S (P = 0.000) and Groups O and T (P = 0.001) but not between Groups T and S (P = 0.460). The differences across the groups were not statistically significant in terms of incidence of intraoperative hypotension, bradycardia, and the cumulative amount of ephedrine consumed. **Conclusion:** This study demonstrated that ondansetron is superior to tramadol in preventing shivering under spinal anesthesia in women undergoing cesarean section.

Keywords: *Ondansetron, shivering, subarachnoid block, tramadol*

Received: 12-Dec-2018;
Revision: 21-Mar-2019;
Accepted: 21-Jan-2020;
Published: 04-May-2020.

Introduction

Shivering is a common, undesirable perioperative event in patients undergoing cesarean delivery under spinal anesthesia.[1,2] Perioperative shivering has a multitude of deleterious effects. These include patients' discomfort, an increase in oxygen consumption up to 500%, and increased risk of myocardial ischemia.[3] Shivering also induces artifacts in intraoperative monitoring especially with electrocardiogram (ECG), noninvasive blood pressure monitoring, and pulse oximetry.[4]

The mechanism of spinal anesthesia-induced shivering is poorly understood. One proposed mechanism is that during spinal anesthesia, there is a block in sympathetic flow which leads to peripheral vasodilatation and increased cutaneous blood flow below the level of

Access this article online

Quick Response Code:

Website: www.njcponline.com

DOI: 10.4103/njcp.njcp_641_18

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How to cite this article: Nnacheta TE, Onyekwulu FA, Amucheazi AO. Prevention of postanesthetic shivering under subarachnoid block for cesarean section: A randomized, controlled study comparing tramadol versus ondansetron. Niger J Clin Pract 2020;23:619-25.

block.[5] There is, subsequently, a core-to-periphery heat redistribution with an increased heat loss to the environment. With a drop in body core temperature, the anterior hypothalamic thermoregulatory thermostat is reset and shivering response is triggered above the level of block with the aim of raising metabolic heat production and core body temperature.[5]

Physical and pharmacological measures have been applied in the prevention and treatment of postspinal shivering. The physical measures are essentially aimed at attenuating perioperative core hypothermia. They include application of radiant heat, use of warm ambient air, use of heated blankets, and use of warm intravenous fluids. These physical methods are however cumbersome, expensive, and yield limited success in preventing shivering.[6]

Pharmacological agents that have been used in the prevention or control of shivering include opioids such as pethidine, tramadol, and butorphanol.[7] Majority of these pharmacological agents have undesirable effects, which make them unsuitable for use as anti-shivering agents in the parturient. Others include ondansetron, ketamine, magnesium sulfate, and alpha2-receptor agonists such as clonidine.[6,8]

Ondansetron, a 5HT3 receptor antagonist, has generated much interest because of its excellent pharmacological profile. It is a drug with a wide therapeutic index and so is devoid of toxicity even in moderately supraclinical doses.[9]

This study was designed to compare the efficacy of ondansetron to that of tramadol in preventing postanesthetic shivering in a population of Nigerian women undergoing cesarean section under subarachnoid block.

Subject and Methods

This prospective, double-blind, placebo-controlled, randomized study was carried out at a tertiary hospital in Nigeria. Pregnant women at term who presented for both elective and emergency cesarean section were recruited for the study. Ethical clearance was obtained from the Health Research Ethics Committee of the institution and informed consent was obtained from the patients. Data were collected over 10 month starting January to October 2014.

Setting the power of study at 80%, the confidence level at 95% and the degree of precision at 10%, the sample size was calculated based on the 15% shivering incidence as recorded by Sule *et al*.[10] in their study. Thus a total of 109 patients aged 18-45 years with term singleton pregnancy were recruited for the study. They were American Society of Anesthesiologists' (ASA) physical status grade I or II.

During the preoperative visit, after thorough clinical assessment the patients were randomly allocated to three groups according to the study drugs, namely tramadol 50 mg group (Group T), ondansetron 4 mg group (Group O), and saline 4 ml group (Group S) using envelope randomization. Pieces of papers were labeled with one of the letters S, T, or O and packaged in small uniform nontransparent envelopes such that each envelope contained one piece of labeled paper. Equal numbers of these small envelopes were shuffled and gathered into a big envelope. Each patient picked a small envelope from inside the big envelope and this determined the group allocation of the patient. An anesthetic assistant then subsequently prepared the study drug according to the patient's group allocation. For each patient, the appropriate study drug was prepared and diluted (clear and transparent solution) to a volume of 4 ml (in a 5 ml syringe). The researcher was unaware of the patients' group allocation.

In the theatre intravenous access was obtained using size 16 gauge intravenous cannula. The baseline vital signs were taken namely: tympanic membrane temperature using digital infrared ear thermometer (ThermoBuddy, HuBDIC200, Korea); noninvasive blood pressure, mean arterial pressure, pulse rate, and oxygen saturation using a multiparameter monitor (Mindray PM-7000, Shenzhen Mindray Biomedical Electronics Ltd, China). The operating room temperature was maintained between 24 and 26°C by adjusting the temperature setting of the air conditioner while measuring the ambient temperature with a wall thermometer (kadio3806, China). Tympanic membrane temperature of less than 36.5°C was defined as hypothermia.

An anesthetic machine with oxygen supply, airway devices, laryngoscope, and resuscitation drugs were available in the theatre. Each patient was preloaded with 20 ml/kg normal (0.9%) saline at room temperature over 10-15 minutes prior to induction of spinal anesthesia. The fluid infusion was subsequently reduced and regulated as required.

After placing the patient in the sitting position with feet on a stool, the anesthetist scrubbed and gloved. The patients' back was cleaned with antiseptics and locating the lumbar spinal interspaces, spinal anesthesia was instituted at either L3/4 or L4/5 interspaces. Hyperbaric bupivacaine 0.5%, 12.5 mg was injected through a 25 G Quincke spinal needle. The patient was then positioned supine with head and shoulders supported on a pillow and tilted to a 15 degrees left lateral position.

Just after the intrathecal injection, the study drug was given as a single intravenous bolus by an anesthetic assistant. Both the patient and the researcher were blinded to the nature of the particular study drug. The pulse rate, mean arterial pressure (MAP), and peripheral oxygen saturation were recorded at 5 minutes' intervals while tympanic membrane temperatures were recorded at 10 minutes' intervals throughout surgery.

All patients were covered with one layer of sterile surgical drapes over the chest, thighs, and legs during the operation. Sensory block level was assessed with alcohol swab test at 5 minutes' intervals. The presence of shivering was observed and recorded. Shivering was graded according to the scale validated by Tsai and Chu[11] as follows: grade 0 = no shivering, grade 1 = piloerection or peripheral vasoconstriction but no visible shivering, 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.

If after induction of spinal anesthesia and concomitant administration of one of the study drugs, grade 3 or 4 shivering was noted, the prophylaxis was regarded as ineffective and intravenous pethidine 12.5 mg was administered as a rescue drug.

Patients were also monitored for hypotension, bradycardia, sedation, nausea, and vomiting. Hypotension, defined as a decrease in mean arterial blood pressure by more than 20% from baseline value, was treated by crystalloid (normal saline) infusion and if necessary ephedrine was administered in 6 mg intravenous boluses. The total volume of crystalloid used was recorded. The amount of ephedrine given in each group was also recorded. Bradycardia, defined as pulse rate less than 60 beats/minute, was also promptly treated with intravenous atropine once it occurred. The degree of sedation was also assessed on a five-point scale: 1 = fully awake and oriented, 2 = drowsy, 3 = sleepy but arousable to verbal command, 4 = sleepy but arousable to mild physical stimulation, and 5 = sleepy and not arousable by mild physical stimulation. Other side effects, including headache, were noted as they occurred.

After delivery of the baby the APGAR score was taken by the neonatologist who was otherwise unaware of the study solutions given. Immediately after the delivery of the baby, oxytocin 5 iu intravenous bolus was administered to the patient followed by slow infusion of 25 iu in 500 ml normal saline. At the end of the surgery, the patient was moved to the recovery room where her vital signs continued to be monitored.

Statistical analysis

Data were collected with forms designed for the study. Statistical analyses were done using Statistical Package for Social Sciences 20.0 (IBM Corp, Armonk, NY, USA). Demographic characteristics and total operating times were compared across the groups using Kruskal-Wallis test. Analyses of variance (ANOVA) with Tukey's *post hoc* test were applied to compare the study groups in terms of the baseline vital signs, and grades of shivering. Categorical variables were compared across the groups using Chi-square tests. Paired-sample *t*-test was applied to analyze the within-group changes in the operating room temperatures. Results were displayed in tables and graphs and *P* values less than 0.05 were considered to be statistically significant.

Results

One hundred and nine patients were enrolled for this study. Nine patients were excluded from the analysis because five patients had unexpected need for blood transfusion; three patients had inadequate spinal block and had to be converted to general anesthesia; one patient was too apprehensive and had to be sedated with diazepam. A total of 100 patients completed the study (33 in group S, 33 in group T, and 34 in group O).

The three groups were comparable with respect to age, weight, gravidity, exigency of surgery, total operating time, and total volumes of intravenous fluid [Table 1]. They were also statistically similar in terms of the baseline vital signs (pulse rate, mean arterial blood pressure, tympanic membrane temperature, peripheral oxygen saturation) and baseline operating room temperatures [Table 2]. The APGAR scores of the newborn [Table 3] were statistically comparable among the groups.

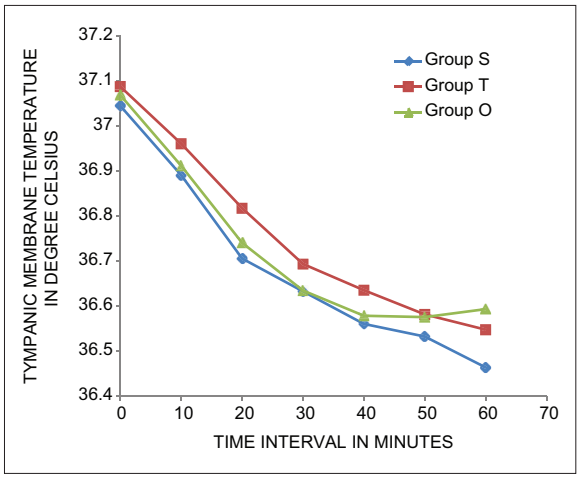

Figure 1: Mean tympanic membrane temperatures at time intervals across the study groups

Table 1: Patients' demographic variables, total operating times, and intravenous fluid volumes

	Group S (*n*=33)	Group T (*n*=33)	Group O (*n*=34)	*P*
Age in years (Mean (SD)*)	33.4 (5)	31.5 (5)	31.3 (6)	0.26
Weight in kg (Mean (SD)*)	76.7 (4)	78.5 (6)	77.2 (5)	0.63
Gravidity (Primigravida/Multigravida)	6/27	5/28	4/30	0.77
Surgical exigency (Elective/Emergency)	13/20	16/17	12/22	0.54
Operating time in minutes (Mean (SD)*)	74.1 (11)	81.3 (11)	76.2 (11)	0.05
Intravenous fluid volume in liters (Mean (SD)*)	3.0 (0.2)	3.0 (0.2)	3.1 (0.2)	0.05

*SD=Standard Deviation

Table 2: Baseline vital signs and baseline operating room temperature

	Group S (*n*=33)	Group T (*n*=33)	Group O (*n*=34)	*P*
Pulse rate in beats/min (Mean (SD)*)	87.8 (13.1)	88.7 (12.3)	93.8 (14.8)	0.28
Mean arterial pressure in mmHg (Mean (SD)*)	89.9 (8.8)	87.7 (6.2)	89.8 (3.3)	0.34
Tympanic temperature in oC (Mean (SD)*)	37.1 (0.3)	37.1 (0.3)	37.0 (0.3)	0.52
SPO_2 in % (Mean (SD)*)	96.3 (1.3)	96.3 (2.1)	96.3 (1.6)	0.99
Operating room temperature in oC (Mean (SD)*)	24.0 (0.4)	24.1 (0.6)	24.1 (0.4)	0.66

*SD=Standard Deviation

Table 3: APGAR scores of the newborn compared across the study groups

	Group S (*n*=33)	Group T (*n*=33)	Group O (*n*=34)	Chi-square	*P*
APGAR 6	1 (3.0%)	0	0	2.05	0.36
APGAR 7	5 (15.2%)	3 (9.1%)	2 (5.9%)	1.64	0.44
APGAR 8	11 (33.3%)	8 (24.2%)	14 (41.2%)	2.17	0.34
APGAR 9	12 (36.4%)	13 (39.4%)	9 (26.5%)	1.37	0.50
APGAR 10	4 (12.1%)	9 (27.3%)	9 (26.5%)	2.81	0.25

Shivering was observed in 16 (48.5%) of the patients in the placebo group [Table 4], while the observation was made in 13 (39.4%) patients in the tramadol group and in only 2 (5.9%) of the patients in the ondansetron group. The differences in incidence of shivering were statistically significant between groups S and O ($P < 0.001$) and groups T and O ($P < 0.01$) but not between groups S and T (p = 0.46).

The overall incidence of shivering in this study was 31%. Of the 13 patients that shivered in group T: 8 had grade 2 shivering while 5 had grade 3 shivering. Of the two patients that shivered in group O: 1 patient each had grade 1 and grade 2 shivering respectively. In contrast, all the 16 cases of shivering in the placebo group were grade 3.

Hypotension occurred most in placebo group and least in tramadol group. Hypotension was noted in 18 (54.5%) patients in group S, 13 (39.4%) patients in group T and 17 (50.0%) patients in group O. Though more patients had hypotension in group O than in group T, patients in group O had the fastest response to fluid boluses. Consequently, cumulative ephedrine consumption was least in group O (42 mg) compared to groups S (102 mg) and T (54 mg). Of the 18 patients who had hypotension in group S, 12 (66.7%) needed ephedrine to control their hypotension while in 6 (33.3%) hypotension was treated with fluid resuscitation alone. Of the 13 patients that had intraoperative hypotension in the tramadol group, 7 (53.8%) needed ephedrine while 6 (46.2%) did not. In the ondansetron group, 5 (29.4%) out of the total of 17 cases of intraoperative hypotension needed ephedrine while 12 (70.6%) responded to fluid resuscitation alone. The differences across the groups were not statistically significant in terms of incidence of intraoperative hypotension (p = 0.45), proportion that required ephedrine (p = 0.11), and the cumulative amount of ephedrine consumed (p = 0.30).

Intraoperative bradycardia occurred in 4 (12.1%), 1 (3.0%), and 2 (5.9%) of patients in groups S, T, and O respectively. There was no statistically significant differences in occurrence of bradycardia across the three groups (p = 0.33). The incidence of side effects (arousable sedation, headache, nausea, and vomiting) among the study groups showed that the incidence of sedation was highest in group T (11, 33.3%). There were equal incidences of sedation (6 patients each) in both the S and O groups. This amounts to 18.2% of patients in group S and 17.6% of patients in group O. The differences in the incidence of sedation were not statistically significant among the groups (P = 0.23).

Five (15.2%) patients complained of headache in the O group while only 1 (3.0%) patient had similar complaint from the T group. All patients in group S were headache-free. A statistically significant difference exists (p = 0.03) when the numbers that had headache were compared among the study groups.

There was no incidence of nausea and vomiting in the ondansetron group. Six (18.2%) and five (15.2%)

Table 4: Number of patients with shivering compared across the study groups

	Number of patients with shivering	Mean rank	Sum of ranks	Mann-Whitney U value	*P*
Group S VS Group T	16 (48.5%)	35.0	1155.0	495.0	**0.46***
	13 (39.4%)	32.0	1056.0		
Group S VS Group O	16 (48.5%)	41.2	1361.0	322.0	**0.000***
	2 (5.9%)	27.0	917.0		
Group T VS Group O	13 (39.4%)	39.7	1310.0	373.0	**0.001***
	2 (5.9%)	28.5	968.0		

**P* values less than 0.05 is statistically significant

patients in group S and group T respectively had nausea without retching or vomiting. The highest incidence of vomiting was recorded in group T (6, 18.2%) followed by group S (2, 6.0%). There were statistical differences among the groups when compared for nausea (p = 0.04) and vomiting (p = 0.02).

Compared to the baseline, the mean operating room temperatures did not change significantly over the period of operation. The *P* value for the changes (temperature) within each group was 0.05 in group S, 0.30 in group T, and 0.19 in group O. Intraoperatively, there was significant drop in the mean tympanic membrane temperature compared to the baseline in all the groups. The drop was more precipitous in groups S and O than in group T [Figure 1]. However, an interesting pattern was observed in group O as the core temperature dropped to its nadir in 40 minutes, after which it was seen to have started rising towards the baseline [Figure 1]. The least incidence of intraoperative hypothermia was recorded in group T (4, 12.1%) compared to group O (7, 20.6%) and group S (14, 42.4%).

Discussion

An important finding in this study was the effectiveness of ondansetron in preventing shivering after spinal anesthesia for cesarean section. This result is similar to other studies.[5,12] Although Kelsaka and colleagues[12] used 8 mg intravenous ondansetron in their study, a slightly higher percentage of patients in the ondansetron group had shivering (8% compared to 5.9% in this study). This may be due to their lower operating room temperature (21-22°C). This, however, has to be interpreted with caution since, contrary to expectation a lower percentage of patients had shivering in their control group compared to the control group of this study (36% vs 48.5%). The differences in patient population in the two studies (nonobstetric versus obstetric patients) could also have accounted for the difference.

Furthermore, in the study on nonobstetric patients by Shakya and co-workers[5] a 10% incidence of postspinal shivering was noted in the ondansetron group. The chronology of patient population, dose of ondansetron, and the subsequent rate of shivering in the three different studies suggest a heightened sensitivity of obstetric population to intravenous ondansetron.

In this study, fewer patients shivered in the tramadol group compared to the placebo group, but the difference was not statistically significant (p = 0.46). This is contrary to the findings in the study by Atashkhoyi and colleagues[13] who observed that tramadol was clinically superior to placebo in preventing postspinal shivering. However, 1 mg/kg tramadol was used in their study unlike in this study where a uniform dose of 50 mg tramadol was used irrespective of the patient's weight. The weight-based dosing of tramadol might have contributed to the increased effectiveness of tramadol in prevention of shivering in their study.

This study demonstrated that ondansetron was more effective than tramadol in preventing shivering. This is contrary to the study done by Ejiro and co-workers[14] were larger proportion of patients had shivering in the ondansetron group compared to tramadol group. Unlike in this study where the study drugs were administered just after induction of spinal anesthesia, Ejiro and colleagues[14] had a delay time of 2 minutes. No reason was given for the delay; and only patients scheduled for elective cesarean section were recruited. It has been suggested that labor has some protective effect on shivering by virtue of labor-induced increase in circulating levels of catecholamines and subsequent augmentation of metabolic heat.[15] This could partly explain the lower incidence of shivering recorded in the ondansetron group in this study compared to their study. However, the overall incidences of shivering were similar in both studies (31% vs 30%).[14]

In this study, the mean core body temperatures dropped below the baseline values in all the groups with the steepest drop noted in the saline group. It was observed that for the tramadol and saline groups, the core body temperature dropped progressively below the baseline. For the ondansetron group, the downward trend in the mean body core temperature ended after 40 minutes. After which the temperature started to appreciate toward the baseline, an indication of recovery of

the thermoregulatory system. It is not clear by what mechanism ondansetron influences the changes in thermoregulation during anesthesia and surgery. However, serotonergic activity has been identified in the anatomic and physiologic pathways of both central and peripheral thermoregulation.[16]

In this study, the highest incidence of sedation (33.3%) was observed in the tramadol group. This is low compared to that reported by Neeharika *et al*.[17] (56.7%) among patients given intravenous tramadol for prevention of shivering during lower limb surgery under spinal anesthesia in India. This may be due to the relatively higher dose of tramadol (1 mg/kg) used for that study.

An adverse effect observed in the ondansetron group was mild headache, which resolved spontaneously within minutes of onset without treatment. There was no record of nausea and vomiting in the ondansetron group in this study. This is in line with the antiemetic property of ondansetron.[18] Ondansetron group demonstrated a superior hemodynamic profile compared to the tramadol and saline groups since cumulative ephedrine consumption was lowest in ondansetron group. This is similar to findings by Sahoo and colleagues.[19] The ability of ondansetron to antagonize the activity of serotonin on the serotonergic (5HT) receptors in the Bezold-Jarisch reflex pathway may explain its ability to attenuate the hypotensive and bradycardic response to spinal anesthesia.[20]

A limitation of the study was that the exact temperature of the crystalloid infusion used was difficult to monitor in the study. However, all crystalloids were not warmed and were kept outside the operating room until they were ready to be used.

Conclusion

This study demonstrated that ondansetron is superior to tramadol in preventing shivering under spinal anesthesia in women undergoing cesarean section. Side effect profile was also better with ondansetron than with tramadol as fewer patients had sedation, nausea, and vomiting in the ondansetron group.

This study could not establish a direct causal relationship between core hypothermia and shivering during spinal anesthesia.

Acknowledgements

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Giovani de Figueiredo L. Incidence of shivering after cesarean section under spinal anesthesia with or without intrathecal sufentanil: A randomized study. Rev Bras Anesthesiol 2012;62:678-84.
2. He K, Zhao H, Zhou HC. Efficiency and safety of ondansetron in preventing postanaesthesia shivering. Ann R Coll Surg Engl 2016;98:358-66.
3. Nallam SR, Cherukuru K, Sateesh G. Efficacy of intravenous ondansetron for prevention of postspinal shivering during lower segment cesarean section: A double-blinded randomized trial. Anesth Essays Res 2017;11:508-13.
4. Badawy AA, Mokhtar AM. The role of ondansetron in prevention of post-spinal shivering in obstetric patients. Egypt J Anaesth 2017;33:29-33.
5. Shakya S, Chaturvedi A, Sah BP. Prophylactic low dose ketamine and ondansetron for prevention of shivering during spinal anesthesia. J Anaesth Clin Pharmacol 2010;26:465-9.
6. Usha S, Kiram M, Prabhakar T. Comparative study of effect of clonidine and tramadol on post-spinal anaesthesia shivering. Indian J Anaesth 2011;55:242-6.
7. Bharti N, Dontukurthy S, Bala I, Singh G. Postoperative analgesic effect of intravenous clonidine compared with clonidine administration in wound infiltration for open cholecystectomy. Br J Anaesth 2013;130:1093-9.
8. Honarmad A, Safavi MR. Comparison of prophylactic use of midazolam, ketamine and ketamine plus midazolam for prevention of shivering during regional anaesthesia. Brit J Anaesth 2008;101:557-62.
9. Wang W, Song X, Wang T, Zhang C, Sun L. 5-HT_3 receptor antagonists for the prevention of perioperative shivering: A meta-analysis. J Clin Pharmacol 2017;57:428-39.
10. Sule AZ, Isamade ES, Ekwempu CC. Spinal anaesthesia in lower abdominal and limb surgery: A review of 200 cases. Nig J Med Res 2005;7:226-30.
11. Tsai YC, Chu KS. A comparison of tramadol, amitriptyline and meperidine for post-epidural anesthesia shivering in parturients. Anesth Analg 2001;93:1288-92.
12. Kelsaka E, Sibel B, Deniz K, Binnur S. Comparison of ondansetron and meperidine for prevention of shivering in patients undergoing spinal anesthesia. Reg Anesth Pain Med 2006;31:38-47.
13. Atashkhoyi S, Negargar S. Effect of tramadol for prevention of shivering after spinal anaesthesia for caesarean section. Res J Biol Sci 2008;3:1365-9.
14. Ejiro BA, Edomwonyi NP, Imarengiaye CO. Ondansetron versus tramadol in preventing postanaesthetic shivering following

caesarean section under spinal anaesthesia. Afr J Anaesth Int Care 2014;14:199-202.

15. Panzer O, Ghazanfari N, Sessler DI, Yucel Y, Greher M, Akca O, *et al*. Shivering and shivering-like tremor during labor with and without epidural analgesia. Anesthesiology 1999;90:1609-16.
16. Cano G, Passerin AM, Schiltz JC, Card JP, Morrison SF, Sved AF. Anatomical substrates for the central control of sympathetic outflow to interscapular adipose tissue during cold exposure. J Comp Neurol 2003;460:303-26.
17. Neeharika A. Prophylactic tramadol versus dexmedetomidine for prevention of shivering during spinal anaesthesia. Int J Sci Study 2014;2:17-20.
18. Rai S, Verma S, Pandey HP, Yadav P, Patel A. Role of butorphanol and ondansetron premedication in reducing postoperative shivering after general and spinal anesthesia: A randomized comparative study from North India. Anesth Essays Res 2016;10:319-23.
19. Sahoo T, SenDasgupta C, Goswami A, Hazra A. Reduction in spinal-induced hypotension with ondansetron in parturients undergoing caesarean section: A double-blind randomized, placebo-controlled study. Int J Obstet Anesth, 2012;21:24-8.
20. Warltier CD, Campagna JA, Carter C. Clinical relevance of Bezold-Jarisch reflex. Anesthesiology 2003;98:1250-60.