

ORIGINAL ARTICLE

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Ondansetron versus Ketamine to control intra-op and post-op shivering caused by subarachnoid block: A comparative phase study**Tabish Hussain¹, Khan Karim Afridi², Asifa Anwar Mir¹**¹ Department of Anesthesia, Critical Care and Pain Medicine, Fauji Foundation Hospital, Kallar Kahar, Pakistan² Department of Surgery, Type D Hospital, Katlang, Mardan, Pakistan

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Abstract

Shivering is a common problem during anaesthesia. Ketamine has been used for preventing shivering during anaesthesia. Ondansetron (8 mg) has been recently evaluated for its peri-operative anti-shivering effect in patients undergoing spinal anaesthesia. The objective of my study is to compare low dose Ondansetron with low dose Ketamine among patients undergoing spinal anesthesia in elective surgery in terms of frequency of shivering. Patients undergoing elective general surgical procedures at Department of Anesthesiology, Holy Family Hospital, Rawalpindi, were inducted in the study. The study design was a randomized control trial and conducted from Jan 2016 to June 2016. Patients were included through a consecutive non-probability sampling. After spinal anaesthesia, patients were randomly assigned to receive Ketamine 0.25 mg/kg (group A) or Ondansetron 4mg (group B) by lottery method. During surgery, shivering was recorded at 10 min interval and recorded in terms of frequency. Out of the total 256 study participants, 128 patients in each group received the study drug (Ondansetron/ Ketamine) before surgery for prevention of shivering. Overall, there were 158 male and 98 female patients. The mean age of study population was 36 ± 11 yrs (range 21–40 yrs). Shivering occurred in 11 (4.3%) patients only. There was no significant difference between the gender distributions between the two groups ($p=0.16$). Patients pre-treated with Ketamine significantly experienced lesser shivering episodes than Ondansetron group (2 (1.6%) vs. 9 (7%), $p=0.03$). The findings of our study suggest that the prophylactic administration of low dose Ketamine (0.25 mg/kg) and Ondansetron (4mg) produces anti-shivering effect in patients undergoing spinal anaesthesia Ketamine (0.25 mg/kg) is significantly more effective than Ondansetron (4mg) during spinal anaesthesia.

Keywords: Ketamine, ondansetron, shivering**Introduction**

Shivering is very unpleasant, physiologically stressful for the patient after surgery, and some patients find the accompanying cold sensation to be worse than the surgical pain. Though the mechanism of origin of shivering is not clear, various hypotheses have been proposed to explain its occurrence [1].

Shivering occurs as a thermoregulatory response to hypothermia or muscle activity with tonic or clonic patterns, and various frequencies have been noticed. However, in the postoperative period, muscle activity may be increased even with normothermia, suggesting that mechanisms other than heat loss with subsequent decrease in the core temperature contribute to the origin of shivering. These may be uninhibited spinal reflexes, sympathetic over-activity, postoperative pain, adrenal suppression, pyrogen release and respiratory alkalosis [2].

Post Anaesthesia Shivering (PAS) occurs in 40% of patients recovering from anaesthesia. Most of the times, it is preceded by central hypothermia and peripheral vasoconstriction indicating that it is almost always thermoregulatory mechanism, which even today is ill understood. Some shivering may not be thermoregulatory, thus making the management of PAS complex. The physiology of PAS, organization of the thermoregulatory mechanism, various measures for prevention and the methods both pharmacological and non pharmacological, of effective managements are reviewed in this article.

Despite the availability of various drugs and technologies to prevent hypothermia it continues to remain an ongoing problem in the peri-operative period. First of all this goal will be to review the organization of the thermoregulatory system, and particularly the physiology of post-anaesthetic shivering, followed by discussion considering consequences, preventive and curative measures [3].

Shivering is defined as an involuntary, repetitive activity of skeletal muscles. The mechanisms of shivering in patients undergoing surgery are mainly intraoperative heat loss, increased sympathetic tone, pain, and systemic release of pyrogens. The median incidence

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of shivering related to regional anesthesia observed in a review of 21 studies is 55% [4].

Shivering increases oxygen consumption, lactic acidosis, carbon dioxide production, and metabolic rate by up to 400%. Therefore, shivering may cause problems in patients with low cardiac and pulmonary reserves. The best way to avoid these intraoperative and postoperative shivering-induced increases in hemodynamic and metabolic demands is to prevent shivering in the first place [4].

Post-anesthetic shivering is spontaneous, involuntary, rhythmic, oscillating, tremor-like muscle hyperactivity that increases metabolic heat production up to 600% after general or regional anesthesia. Post anesthetic shivering may cause discomfort to patients, and aggravate wound pain by stretching incisions and increase intracranial and intraocular pressure. Regional anesthesia produces vasodilatation, which facilitates core-to-peripheral redistribution of heat and the cool periphery is warmed at the expense of the core compartment. Thus, hypothermia from epidural anesthesia results from redistribution of heat from the core to the periphery [5].

Spinal anaesthesia is widely used as a safe anaesthetic technique for both elective and emergency operations. Shivering is known to be a frequent complication, reported in 40 to 70% of patients undergoing surgery under regional anaesthesia. Shivering is a potentially serious complication, resulting in wound infection; increased surgical bleeding; and morbid cardiac events [6].

Shivering associated with spinal anesthesia is a frequent event, and the reported median incidence of shivering related to neuraxial anesthesia is up to 55%. The mechanism of shivering in patients undergoing spinal anesthesia is not clear, but hypothermia due to redistribution of heat caused by vasodilation below the level of a neuraxial block is suggested [6].

Material and Methods

This randomized control trial study was conducted at Holy Family Hospital, Rawalpindi for a period of 6 months from Jan 2016 to June 2016. A total of 256 patients were recruited in the study and were divided into two groups of 128 patients each by using consecutive non probability method..

- **Inclusion criteria:**

- o ASA – I (normal healthy patient), II (mild systemic disease with no functional limitation).
- o Age: Adults, 20-40 years.
- o Elective general surgical patients

- **Exclusion criteria:**

Patients with concomitant co-morbid conditions like diabetes mellitus, hypertension, Ischemic Heart Diseases, pulmonary, hepatic or renal diseases diagnosed on history and clinical examination.

- o Contraindication to Regional anaesthesia.(like coagulopathies ,infection at injection site, hypovolemia).
- o Contraindications for using Ondansetron and ketamine (Allergic reactions/hypersensitivity).

Data Collection Procedure

After taking approval from hospital ethical committee, 256 patients were included in this study according to selection criteria mentioned above. Patients were assessed for anaesthesia fitness a

day before surgery and no oral intake was allowed for at least 8 hrs before surgery. Written informed consent was taken. Patients were randomly divided in group A and B by lottery method. All the patients were given premedication with 0.2 mg/kg of diazepam at night before surgery. In the operating room, routine standard monitoring protocols were followed in all patients. The temperature of operating room was maintained at 24-26°C with the help of air conditioner temperature setting. The perioperative temperature of patients included in the study was same as of Operation Theater i.e. 24-26 degrees. Since all the cases were dealt in the operation complex that has centralized temperature control system, so all the units in complex including pre-op room, preparation room, operation room, postoperative recovery room, ICU, CCU ,level 1 and 2 recovery has fixed standard protocols and temperature settings.

Before spinal anesthesia, each patient was preloaded with 10-15 ml/kg of the Ringer Lactate solution. Subarachnoid block was instituted at either L3-L4 interspace with 2 ml of 0.75% hyperbaric Bupivacaine in sitting position, the average time of this anesthesia is 90-120 minutes. Also the individual cases of surgery involved below umbilicus operations either hernia repair (inguinal/femoral/paraumbilical) or varicose veins, so the average time of surgical procedure was standard 60-90 minutes. So in conclusion, standardization was maintained in terms of duration and type of anesthesia and surgery among all the included study participants. Axillary temperature was measured with the help of axillary thermometer every 20 minutes till end of the surgical procedure. The intravenous fluid at room temperature (24°C- 26°C) was infused and all the patients were covered with standard single blanket. Just after the intrathecal injection, one of the study drugs (Ondansetron 4 mg/ Ketamine 0.25 mg/kg) was given as IV bolus. Shivering was recorded at 10 min interval per-operatively and recorded in terms of frequency. Data was entered and analysed in SPSS (17.0). Mean $\pm$ standard deviation was calculated for quantitative variables like Age & BMI. Frequency and percentages were calculated for qualitative variables like gender and shivering. Chi- square test was used to compare shivering in both groups. $P < 0.05$ was taken as level of significance.

Results

Out of the total 256 study participants, 128 patients in each group received the study drug (Ondansetron/ Ketamine) before surgery for prevention of shivering. Overall, there were 158 male and 98 female patients. The mean age of study population was approximately 36 ± 11 yrs (range 21-40yrs). Shivering occurred in 11 (4.3%) patients only (Table 1).

The comparison between two groups is given in table 2. There were 58 (36.7%) males in Ketamine group in comparison to 100 (63.3%) males in Ondansetron group. Similarly the female proportion in the study patients was 28.6% (Ondansetron group) and 71.4% (Ketamine group). This gender distribution was similar with significant with $p = 0.0001$. The mean Age (yrs) was not significantly different between the two groups (30.02 ± 05.54 vs. 29.93 ± 05.80 , $p = 0.9$). There was no significant difference between the gender distributions between the two groups ($p = 0.16$) (Graph 1). Patients pre-treated with Ketamine significantly experienced lesser shivering episodes than Ondansetron group; 2 (18.2%) vs. 9 (81.8%), $p = 0.03$, Graph 2).

Table 1. Baseline characteristics of study population

Total no of patients		256
No of patients in each group		128
Gender	Males	158
	Females	98
Mean Age (yrs)		36 ± 11yrs (range 21-40yrs)
Shivering Frequency		11 (4.3%)

Table 2. Comparison of pre-operative ketamine vs. ondansetron in prevention of post-operative shivering

n=256	Ketamine	Ondansetron	P value
Gender			
Males	58 (36.7%)	100 (63.3%)	0.16
Females	70 (71.4%)	28 (28.6%)	
Mean Age (yrs)	30.02 ± 05.54	29.93 ± 05.80	0.9
Shivering			
Present	2 (18.2%)	9 (81.8%)	0.03
Absent	126 (51.4%)	119 (48.6%)	

Discussion

Very few studies are available till date in relation to use of ketamine for prevention of shivering during general or regional anaesthesia probably because of its undesirable side effects like too much sedation, hallucination, nausea and vomiting [10]. In our study, very low dose of ketamine (0.25mg/kg) was used to minimize the side effect and we found that it was significantly effective and the shivering was observed only in 2 patients out of 40 (1.6%).

In our study, 0.25mg/kg of ketamine was also as effective as 0.5 mg/kg of ketamine. In our study, shivering was seen in only two patients (1.6%) with a dose of 0.25mg/kg. In another study, shivering was observed in only one patient (2.5%) in ketamine group when ketamine 0.25mg/kg was used prophylactically during spinal anesthesia [7].

In one study Dal et al. compared placebo, meperidine and ketamine 0.5 mg/kg for prevention of shivering after general anesthesia and found ketamine 0.5 mg/kg to be effective [8]. Although our study was performed on the patients to observe incidence of shivering after prophylactic use of ketamine during spinal anesthesia as compared to patients undergoing general anesthesia in Dal et al. study, our study is better because: first, a lower dose of ketamine (0.25 mg/kg) was used as compared to 0.5 mg/kg ketamine used in this study; second, in comparison to 30 patients who were given ketamine in this study we gave ketamine to 128 patients and third, the low incidence of shivering in this study might be due to effects of general anesthesia.

In our study we investigated the comparative efficacy and safety of prophylactic low dose of Ondansetron and Ketamine (with different mechanism of action) for prevention of shivering during spinal anaesthesia. In this study, shivering was graded using a scale that was validated by Gangopadhyay S et al [9]. The prophylactic drug was considered ineffective if the patient shivered to grade 3 and pethidine 0.5mg kg-1IV was given to control the shivering. Sagir et al [10] and Shakya et al [7] used same protocol in their study. Ondansetron, which is a specific 5-HT₃ receptor antagonist,

is widely used antiemetic drug. The mechanism of action could be related to the inhibition of serotonin reuptake on the pre-optic anterior hypothalamic region. 5-HT₃ receptors may also influence both heat production and heat loss pathways [11].

The recommended dose of Ondansetron for prevention of postoperative nausea & vomiting is 4-8 mg in adult patients [12]. Kelsaka et al [13] compared the 8mg Ondansetron with Pethidine for prevention of shivering and found the same anti-shivering effect and the incidence of shivering was 8% in Ondansetron group. In study by Shakya et al [7], low dose of Ondansetron (4mg) was used and the incidence of shivering was only 10% in the Ondansetron group. In our study, shivering occurred in almost same frequency as given in literature i.e. 7% patients pre-medicated with Ondansetron in a dose of 4mg.

In present study, despite a higher age group in Ketamine treated patients, when the effectiveness of Ondansetron and Ketamine was compared, Ketamine was found to be more effective in prevention of shivering. 9 (7%) vs. 2 (1.6%), p=0.03). The side effects of the drugs, which although are not part of our study objectives, were also no more in Ketamine group as expected from its known pharmacologic properties.

Conclusion

The findings of our study suggest that the prophylactic administration of low dose Ketamine (0.25 mg kg⁻¹) and Ondansetron (4mg) produces anti-shivering effect in patients undergoing spinal anaesthesia. Ketamine (0.25 mg/kg) is significantly more effective than Ondansetron (4mg) during spinal anaesthesia.

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