

Prophylactic low dose ketamine infusion for prevention of shivering during spinal anesthesia: A randomized double blind clinical trial

Ramyavel Thangavelu, Sagiev Koshy George, Ravichandran Kandasamy¹

Department of Anaesthesiology, Pondicherry Institute of Medical Sciences, ¹Department of Biostatistics, Pondicherry Institute of Medical Sciences, Pondicherry, India

Abstract

Background and Aims: Regional anesthesia is known to produce perioperative hypothermia and shivering. We aimed to evaluate if prophylactic low dose ketamine bolus followed by infusion would prevent intraoperative and postoperative shivering under spinal anesthesia.

Material and Methods: Sixty patients belonging to American Society of Anaesthesiologists (ASA) 1 and 2 undergoing abdominal and lower limb surgery were randomized to receive either 0.2 mg/kg iv of ketamine bolus followed by infusion 0.1 mg/kg/hr (Group K) or 5 ml of saline followed by 0.1 ml/kg/hr solution (Group S) as an infusion throughout the period of surgery. The incidence of shivering was the primary outcome of the study with degree of sedation and the hemodynamic profile between the two groups being the secondary outcomes. Hemodynamics (Heart rate, Mean Blood Pressure and temperature), Grade of shivering and grade of sedation were assessed intraoperatively and for grade of shivering and sedation two hours postoperatively. Repeated measures Analysis of Variance (ANOVA) was used to compare the hemodynamic variables and Chi-square test/Fisher's exact test to compare the grades of shivering and sedation between the two groups.

Results: Intraoperative shivering was seen in eighteen patients in saline group (58.06%) and only with four patients (13.79%) with ketamine group ($P < 0.001$). Post operative shivering was also significantly less in ketamine group compared to saline ($P = 0.01$). Also, patients who received ketamine had significant sedation in the intraoperative period ($P < 0.001$).

Conclusion: Prophylactic low dose ketamine administered as a small bolus followed by an infusion was effective in preventing both intraoperative and postoperative shivering.

Keywords: Hypothermia, intraoperative, ketamine, prophylactic, shivering

Introduction

Thermal inputs in humans are integrated at the level of anterior hypothalamus. The normal human body core temperature is 36.5°C to 37.5°C with an interthreshold range between

0.2 to 0.4°C. Any fall in temperature below this set point will activate reflexes to warm the body.^[1] Regional anesthesia produces vasodilation which facilitates core to peripheral redistribution of heat thus triggering vasoconstriction and shivering above the level of block.^[2]

Address for correspondence: Dr. Ramyavel Thangavelu, Department of Anaesthesiology, Pondicherry Institute of Medical sciences, Kalathumettupathai, Ganapathichettikulam, Village 20, Kalapet, Puducherry, India.
E-mail: ramyavel1988@gmail.com

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Shivering under regional anesthesia is influenced by various other factors like number of spinal segments blocked, advanced age, high level of spinal blockade and use of additives in spinal anaesthesia that might influence the regulatory mechanisms.

Perioperative hypothermia and shivering is one of the frequent undesirable, side effects encountered postoperatively. Incidence of shivering with regional anesthesia is 40-60%.^[3] Ketamine, a competitive N- methyl-D-aspartate (NMDA) receptor antagonist has a role in thermoregulation secondary to an inhibition of nor epinephrine uptake into post ganglionic sympathetic nerve endings.^[4,5] Although there are innumerable studies demonstrating use of bolus dose of the drug, literature review did not reveal many studies that had used ketamine infusion for the same purpose. We aimed to study and compare the incidence of intra and postoperative shivering between intravenous low dose ketamine infusion and placebo group. We hypothesized that low dose bolus followed by infusion of ketamine throughout the period of surgery would have its effect on prevention of both intraoperative and postoperative shivering.

Material and Methods

The study is a randomized double-blind controlled trial conducted on 60 patients aged 18–60 years belonging to ASA 1 and 2 undergoing abdominal and lower limb surgery under spinal anesthesia in a tertiary care hospital. The study has been registered with clinical trial registry of India. (CTRI registration no.REF/2017/03/013885). Patients with Body mass index (BMI) >30 kg/m², patients with uncontrolled hypertension, vascular or coronary disease, patients with increased intraocular, intracranial pressure, patients unwilling or uncooperative for spinal anesthesia, known psychiatric or neuromuscular disorders were excluded from the study. Institutional ethical committee clearance (IEC: RC/17/25 dated 4/8/2017) was obtained before initiation of the study. An informed written consent was obtained from all the patients undergoing surgery. All patients were premedicated the night before and morning of surgery with tablet ranitidine, tablet diazepam and tablet perinorm. After transferring to the operation theatre (OT), ASA standard monitors were attached, an intravenous line secured and intravenous preloading with 10 ml/kg Ringer lactate was given. Temperature of the operating room was maintained between 24 and 26°C by adjusting the temperature setting of the air conditioner. Patients were then divided into 2 groups using computer generated randomization:

Group K: Received 0.2 mg/kg iv of ketamine diluted to 5 ml followed by infusion 0.1 mg/kg/hr as a 20 ml solution

Group S: received 5 ml of saline followed by infusion 0.1 ml/kg/hr as a 20 ml solution.

The primary anesthesiologist blinded to the assignments administered drugs to the patient in two groups. Bolus dose of study drug was administered before attempting spinal anesthesia. Spinal puncture was performed in sitting position at the L3-L4 or L4-L5 interspace with a 25 G Quincke's spinal needle. Sterile technique was adopted, and 3 ml of 0.5% hyperbaric bupivacaine was administered via the needle into the subarchanoid space. Patients were then placed in supine position. Spread of sensory block was assessed by pinprick every minute after the block until reaching the T6 dermatome and motor block was evaluated according to Bromage scale. Once adequate block was achieved, study drug infusion was started and continued throughout the period of surgery. Injection ephedrine 6 mg bolus was administered in case off all of MAP >20% from baseline. Nasopharyngeal temperature was monitored using a temperature probe. The second blinded anesthesiologist recorded the following parameters every 5 min for the initial 30 min followed by every 15 min till the end of the surgery. Grade of shivering, Hemodynamics (MAP, HR, RR, temperatue & SpO₂), Degree of sedation. Occurrence of shivering was graded by a scale originally used by Mahajan *et al.*^[6] where:

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.

Based on the Grading of shivering, shivering of at least Grade 3 or more was considered significant and was taken as “presence of shivering”. If 20 minutes after spinal anesthesia and concomitant administration of prophylactic infusion dose of study drug, shivering was present, then the treatment was considered ineffective and Injection Tramadol 1 mg/kg iv was given as the rescue drug.

Degree of sedation was assessed by the attending anesthesiologist using a Five point sedation scale as used by Shakya *et al.*^[7] in his study and graded as –

Grade 1 :fully awake and oriented patient

Grade 2 : drowsy

Grade 3 : eyes closed, arousable on command

Grade 4 : eyes closed, arousable to physical stimuli

Grade 5: eyes closed and un arousable to physical stimuli

The incidence of intraoperative and postoperative shivering were the primary outcomes of the study with degree of sedation

and the hemodynamic profile being the secondary outcomes. Reporting of any hallucination, episodes of nausea, vomiting, headache, nystagmus was noted if present. At the end of surgery, patient was shifted to recovery and followed up for 2 hours.

Statistical analysis

Patients demographic and clinical parameters were recorded. Mean \pm SD were used to express the continuous variables. They were tested for normality using Kolmogorov Smirnov test. Repeated measures ANOVA was used to compare the hemodynamic parameters (HR, SpO₂, MAP, and temperature) over various time intervals. The degree of shivering and sedation was compared between the groups using Chi square/Fisher's exact test. All statistical analysis were carried out at 5% level of significance and a $P < 0.05$ was considered as statistically significant.

Sample size calculation was done from a previous similar study taking incidence of intra operative shivering as the primary outcome.^[7]

In the above study, the incidence of intra operative shivering in saline group was 42.5% and incidence in ketamine group was 2.5%. Taking difference in the incidence between the two groups to be the effect size (40%), a power analysis using continuity correction indicated that a minimum of 21 patients in each group would be needed to reach 80% power with an alpha error of 0.05 to reject null hypothesis. Thus, a total of 30 patients were included in each group to allow for withdrawal/drop out due to various reasons.

Results

A total of 60 patients were enrolled in the study with 29 in ketamine group and 31 patients in saline group.

The two groups were comparable with respect to age, gender, weight, height, duration of surgery and median level of sensory block [Table 1].

Out of 60 patients, shivering was seen in 18 patients in saline group (58.06%) and only in 4 patients in ketamine group (13.79%) ($P < 0.001$) [Figure 1].

The hemodynamic parameters were compared between the two groups at various time points till the end of the surgery. There was no significant difference between the two groups with regard to HR, MAP, and temperature.

Sedation was seen in all the 29 patients in ketamine group (grade 3 or more) and only with 6 patients (19.35%) in saline group, ($P < 0.001$) [Table 2].

Patients were monitored for upto 2hours, postoperatively. Among the patients who had no significant shivering (grade 3 or more) intraoperatively it was found that patients in ketamine group continued to have no shivering as compared to 30.77% saline group of patients who developed significant shivering in the postoperative period ($P = 0.01$).

Aborder line significant sedation was seen in patients with ketamine group as compared to saline in the postoperative period. ($P = 0.049$) [Table 2].

None of the patients in the study experienced hypotension (requiring treatment with vasopressor), nausea, vomiting, headache, hallucination, or nystagmus.

Discussion

Shivering causes increase in metabolic activity, oxygen consumption upto 300–400% and carbon dioxide production. It causes arterial hypoxemia, lactic acidosis, increases intraocular and intracranial pressures, increases cardiac output and peripheral vascular resistance.^[8,9] Perioperative hypothermia and shivering is usually prevented by physical methods such as external heating^[8] or pharmacological intervention (opioids, 5 HT₃ antagonists, NMDA receptor antagonists, cholinomimetics).^[10-12] A large amount of research

Table 1: Comparison of patient characteristics among the two groups

Parameter	Group K (n=29)	Group S (n=31)
Age (years)	36.97 \pm 12.41	40.45 \pm 16.69
Weight (kg)	60.00 \pm 8.90	63.87 \pm 8.89
Height (cm)	157.03 \pm 4.41	160.71 \pm 4.63
Gender (Male/Female)	15/14	14/17
Duration of surgery (min)	89.83 \pm 37.38	91.13 \pm 38.33
Median level of sensory block	T6	T6

Data presented as Mean \pm SD, except for gender. n=Number of patients, SD=Standard deviation. K=Ketamine, S=Saline

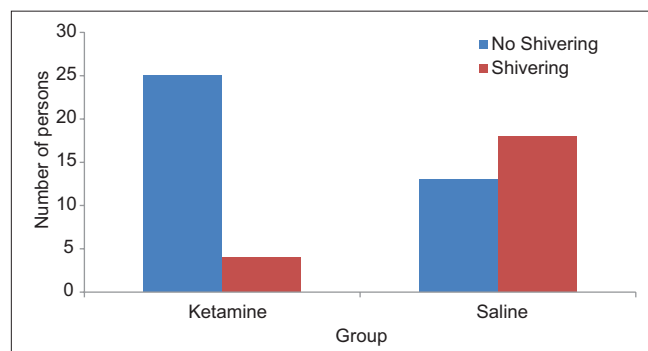


Figure 1: Bar chart showing distribution of patients with shivering among the two groups. Four patients in ketamine group had shivering (Grade 3) as compared to eighteen patients in saline group ($P < 0.001$)

has been done using ketamine in various bolus doses for prevention/treatment of shivering.^[7,13-15] However, literature review did not reveal many studies that had used ketamine infusion for the same purpose. In our study, we used a small bolus dose of ketamine (0.2mg/kg) followed by continuous infusion (0.1mg/kg/hr) throughout the period of surgery for prevention of shivering under spinal anaesthesia.

The incidence of shivering in patients who received saline was 58.06% as compared to only 13.79% in ketamine group. In a study done by Kose *et al.*^[16] in patients undergoing cesarean section, the number of patients experiencing shivering were significantly less in ketamine groups (K 0.25 and K 0.5 group). The anti-shivering property has been attributed to its role in thermoregulation at various levels though the exact anti-shivering mechanism of ketamine is not very clear. Shakya *et al.* used a low dose ketamine bolus of 0.2 mg/kg, a dose similar to that used in our study.^[7] They found that the bolus dose given at the time of spinal anaesthesia effectively reduced shivering in ketamine group intra operatively as compared to ondansetron and saline.

The median level of sensory block after 15 min of spinal anaesthesia was comparable in two groups. There was no difference between the two groups in relation to HR and MAP. The results were consistent with previous studies by Shakiya and Sagir who also showed no difference in hemodynamics between the two groups.^[7,17] Shakya *et al.* had used a bolus dose of ketamine in the dose of 0.25 mg/kg at the beginning of spinal anaesthesia and compared its anti-shivering effect with ondansetron. In our study, the mean values of HR in saline group were consistently higher compared to ketamine group after 90 min; however, the difference did not have any statistical significance. This tachycardia can be attributed to sympathetic stimulation caused by shivering.^[18,19]

Temperature monitoring in our study was done using a temperature probe placed in the nasopharynx. The relationship between shivering and hypothermia is complex and remains unresolved. A study done by Mahajan *et al.* in as early as 1994 suggests the degree of shivering to be unrelated to the axillary temperature.^[6] In our study, there was no difference in the temperature recordings between the two groups. However temperature was preserved in the group which received ketamine compared to ondansetron and saline in the study done by Shakya *et al.*^[7] They attributed this effect to the vasoconstrictive properties of ketamine which decreases the core to peripheral redistribution of heat thereby preventing fall in temperature associated with spinal anaesthesia. However, apart from its peripheral action, Ketamine has also been found to have central effects with modulation of thermoregulation at multiple levels namely hypothalamus

Table 2: Incidence of sedation (Intraoperative and Postoperative) between the two groups

Parameter	Ketamine (n=29)	Saline (n=31)	P
Intraoperative Sedation	29 (100%)	6 (19.35%)	<0.001*
Postoperative Sedation	6 (20.69%)	1 (3.23%)	0.049

n=No of patients. All the patients in ketamine group were sedated as compared to only six patients in the saline group intraoperatively ($P<0.001$). * statistically significant

and locus coeruleus.^[1,20] In our study, both the groups had a fall in temperature following spinal, ketamine by lowering the shivering threshold at the level of hypothalamus prevented shivering whereas patients who received saline continued to shiver as a compensatory mechanism to hypothermia. Ketamine controls shivering by non-shivering thermogenesis either by action on the hypothalamus or by beta adrenergic effect of nor epinephrine.^[11]

Postoperative shivering occurs in 5–65% of patients recovering from anaesthesia.^[9,21] Ketamine has also been found to have a role in decreasing post-operative shivering.^[22]

The effect of bolus dose dissipates after 30–45 minutes and hence its efficacy may not be seen for a long duration after a single bolus dose. Hence in our study, bolus given at induction was followed by a continuous infusion throughout the surgery assuming it would maintain a steady state plasma concentration and also show a steady decline after stopping the drug. Patients were followed up for two hours postoperatively and we found a significant reduction in shivering in patients who received ketamine when compared to saline. Thus we found that the intraoperative small dose infusion confers its anti-shivering benefit postoperatively as well.

In addition to anti shivering benefits of ketamine, it has also been found to be an effective agent in providing sedation and prevents recall.^[23] Sedation (Grade 3) was seen in all the 29 patients in ketamine group and only with 6 patients in saline group. In the study by Shakya *et al.*, though the dose of ketamine used was similar to that used in our study, most of the patients experienced only mild sedation. (Grade 2). This sedative effect might also help to alleviate the anxiety in patients undergoing surgery under spinal anaesthesia.^[24]

Ketamine has a large volume of distribution and accumulates during prolonged infusions and hence patients may be at risk for developing abnormal liver function tests or psychomimetic side effects.^[25] However, studies with 24–72 hr inpatient ketamine infusions show that 0.12–0.2 mg/kg/hr have no increased incidence of psychomimetic effects.^[26]

Hallucination is one of the known side effects of ketamine but has been reported only with large doses.^[15] Sharma and colleagues^[15] demonstrated that ketamine (0.5 mg/kg) was useful in treatment of post anesthetic shivering but 2 out of 30 patients developed hallucinations and 4 patients developed delirium. None of the patients experienced hallucination with the dose used in our study.

The limitation of the study being only grade 3 shivering was considered significant and was recorded as presence of shivering and rescue medication was administered. Though recording of grade 1 and grade 2 shivering was done, it was considered in significant.

Conclusion

Prophylactic Low Dose ketamine administered as a small bolus followed by an infusion produces a significant anti-shivering effect both intraoperatively and postoperatively compared to placebo without any significant side effects.

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Conflicts of interest

There are no conflicts of interest.

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