

A placebo-controlled comparison of ketamine with pethidine for the prevention of postoperative shivering

Dar AM, MBBS, Postgraduate Scholar

Qazi SM, MBBS, MD, Additional Professor

Sidiq S, MBBS, MD, Senior Resident

Department of Anaesthesiology and Critical Care, Sher-i-Kashmir Institute of Medical Sciences, Soura, India

Correspondence to: Suhail Sidiq, e-mail: sidiqsuhail@gmail.com

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Abstract

Objective: Postanaesthetic shivering is a recognised complication of general and regional anaesthesia. Pharmacological and nonpharmacological methods have been used to prevent shivering. This study was conducted to determine the efficacy of ketamine when compared with pethidine and placebo for the prevention of postanaesthetic shivering.

Design: A randomised, double-blind study was conducted.

Setting and subjects: This study was conducted on 90 American Society of Anesthesiologists (ASA) I and II patients of both genders, aged 18-70 years, who were to undergo surgery under general anaesthesia. Patients were randomised into three equal groups: Group S received a saline placebo, Group P received pethidine 20 mg and Group K received ketamine 0.5 mg/kg. The study medication was given within 20 minutes of the estimated end of surgery.

Outcome measures: Haemodynamic parameters were noted before, during and after anaesthesia. Tympanic temperature was recorded during the intraoperative period, on arrival in the recovery room (T0) and subsequently at 10 minutes (T10), 20 minutes (T20) and 30 minutes (T30). Shivering was graded on a four-point scale. Pain was assessed and recorded by means of a visual analogue scale. Any untoward side-effects were also noted.

Results: The demographic profile of the patients was similar. The number of patients shivering at T0 and subsequently at T10 and T20 was significantly less in Group K and Group P than in Group S (p -value < 0.005). However, there was no difference between Group P and Group K (p -value > 0.005). Thirty minutes after the end of the anaesthetic, there was no difference between the groups (p -value > 0.005). Haemodynamic parameters were similar throughout. The incidence of adverse effects was similar.

Conclusion: Ketamine was found to be as effective as pethidine in preventing postanaesthetic shivering without increasing the risk of side-effects.

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Introduction

Shivering is a significant complication of hypothermia.¹ The most common reason for shivering is cold, but some shivering, including essential tremor, is not thermoregulatory.² The processes that lead to core hypothermia in regional and general anaesthesia are similar.³ All general anaesthetics markedly impair normal autonomic thermoregulatory control.⁴ Shivering may also result from the release of cytokines during the surgical procedure or from postoperative pain.⁴ Shivering occurs in approximately 40%

of unwarmed patients recovering from general anaesthesia, in about 50% of patients with a core temperature of 35.5°C and in roughly 90% of patients with a core temperature of 34.5°C. Inadvertent hypothermia is associated with numerous adverse outcomes in the postoperative period.¹ Shivering is associated with substantial adrenergic activation and discomfort.^{5,6} Shivering can double or even triple oxygen consumption and carbon dioxide production, increasing the chances of adverse myocardial outcomes.⁷ A marked increase in plasma catecholamines levels also contributes to the increased risk of cardiac

complications.⁵ Shivering also increases intraocular pressure⁸ and intracranial pressure.⁹ Interference with the monitoring of heart rate and blood pressure, and an increase in metabolic rate and lactic acidosis, have been described in shivering patients.^{4,10,11} Clinically significant hypoxaemia is seldom seen in association with shivering as the reflex is inhibited by hypoxaemia.¹² Various drugs have been investigated to prevent and treat postoperative shivering, including pethidine, ketansarin, sufentanil, alfentanil, tramadol, physostigmine, urapidil, nefopam, doxapram and nalbuphine.^{4,10,11,13} Of the pharmacological agents, pethidine has been shown to be one of the most effective treatments.¹⁴ Ketamine has also been shown to inhibit postoperative shivering in some studies.¹⁵ This study was a placebo-controlled evaluation of the efficacy of low-dose ketamine compared with pethidine in preventing postoperative shivering.

Material and methods

After receiving approval from the hospital ethics committee and obtaining informed written consent, 90 patients of both genders aged 18-70 years [American Society of Anesthesiologists (ASA) Grade I and II], who were to undergo surgery under general anaesthesia for an anticipated duration of 120-180 minutes, were enrolled in the study. Patients were excluded from the study if they had a history of convulsions, multiple allergies, hypertension, coronary artery disease or other cardiorespiratory or neuromuscular pathology, as well as if they had undergone urological endoscopic procedures.

All patients were informed about the visual analogue scale (VAS) before surgery. The patients were randomly allocated to receive saline (Group S, n = 30), pethidine 20 mg (Group P, n = 30) or ketamine 0.5 mg/kg (Group K, n = 30) intravenously (IV) 20 minutes before the end of surgery. The treatment drugs were prepared, diluted to a volume of 5 ml and presented as coded syringes by an anaesthetist who was not involved in the management of the patients. Heart rate, blood pressure and saturation of peripheral oxygen (SpO₂) were recorded before and during the surgery. Tympanic temperature was measured before anaesthesia, immediately after induction, 30 minutes after induction and before administration of the study drug. Anaesthesia was induced with sodium thiopentone 4-6 mg/kg, morphine 0.1 mg/kg and atracurium 0.5-0.6 mg/kg for orotracheal intubation. It was maintained with N₂O 60% in O₂ and isoflurane. Warm IV fluids were used intraoperatively. Approximately 20 minutes before completion of the surgery, the patients were randomly assigned to receive the study drug. The type of anaesthesia and the type and duration of surgery were recorded. Postoperatively, patients received oxygen via face mask and were covered with blankets. An anaesthetist who

was unaware of which study drug had been administered observed the patients for shivering, pain, nausea, vomiting, heart rate, blood pressure, SpO₂ and tympanic temperature, which was measured and recorded at T0 and subsequently at T10, T20 and T30.

Shivering was graded using a four-point scale:

- Grade 0: No shivering
- Grade 1: Mild fasciculations of the face or neck
- Grade 2: Visible tremors that involved more than one muscle group
- Grade 3: Gross muscular activity that affected the entire body.

VAS score assessment, in which "0" reflected no pain and "10" the worst pain imaginable, was carried out on admission to the recovery room and then at the first hour and second hour. Any possible side-effect, e.g. nausea, vomiting, hypotension, tachycardia, hypertension or hallucinations, was noted. Postoperative pain was treated with morphine 0.05 mg/kg. Shivering was treated with pethidine 20 mg IV if the shivering grade was ≥ 2 . Statistical analysis was performed using the Statistical Package for the Social Sciences[®]. Mean differences between the three groups regarding age, weight and height were tested using analysis of variance. The χ^2 test was used to analyse the difference between gender, ASA class, number of patients who shivered and patients with adverse effects. A p-value of < 0.05 was taken to be significant. Post hoc comparisons were performed using Bonferroni correction of significance level. Power analysis showed that a sample size of 30 per group would achieve 93% power in an χ^2 test with a significance level of 0.01 at group proportions of 0.6 and 1.

Results

All three groups were comparable with respect to age, gender, weight, height and ASA status (see Table I).

However, a comparison of shivering between Group K and Group P showed no difference between them at any point in time (Table III).

Statistical analysis of the haemodynamic parameters of the three groups at regular intervals showed no difference (p-value > 0.005). Comparison of the intraoperative and postoperative tympanic membrane temperatures showed no statistical difference (p-value > 0.005) at any point in time. The mean time of rescue analgesia was shorter in Group S (45 \pm 12 minutes) than in Group K (70 \pm 18 minutes) and Group P (77 \pm 20 minutes). One patient each from Group P and Group S had hypotension, one patient each from Group P and Group S had hypertension and two patients from Group K had intraoperative hypertension. Only one patient from Group K had hallucinations. Nausea and vomiting were observed in one patient in each group. None of the

Table I: Demographic profile of the patients

Demographic characteristics	Group S	Group P	Group K
Age (years)	38.70 ± 1.7	39.7 ± 1.5	36.63 ± 1.2
Gender (male:female)	22:8	21:9	20:10
Weight (kg)	63.07 ± 2	63.40 ± 1.8	63.78 ± 2
Height (cm)	169 ± 3	171 ± 4	170 ± 3
ASA (Grade I:II)	28:2	27:3	28:2

The number of patients with postoperative shivering at T0, and then at T10 and T20, were significantly less in Group P and Group K than in Group S (Table II). In Group S, 18 patients (60%) had shivering ≥ grade 2. In Group P, two patients (7%) had shivering ≥ grade 2. In Group K, three patients (10%) had shivering ≥ grade 2.

Table II: The number of patients with different grades of shivering in the three treatment groups

Grade 0, 1, 2 and 3				
Time	Group S	Group P	Group K	p-value
T0	16/7/3/4	28/1/1/0	29/1/0/0	0.001
T10	15/6/3/6	29/0/1/0	28/1/1/0	0.000
T20	24/5/1/0	28/2/0/0	28/1/1/0	0.002
T30	26/3/1/0	29/1/0/0	28/1/1/0	0.597

T0: On arrival in the recovery room, T10: Subsequently at 10 minutes, T20: Subsequently at 20 minutes, T30: Subsequently at 30 minutes

Table III: Comparison of shivering between Group K and Group P

Time	Group K	Group P	p-value
T0	29/1/0/0	28/1/1/0	0.601
T10	28/1/1/0	29/0/1/0	0.601
T20	28/1/1/0	28/2/0/0	0.513
T30	28/1/1/0	29/1/0/0	0.601

T0: On arrival in the recovery room, T10: Subsequently at 10 minutes, T20: Subsequently at 20 minutes, T30: Subsequently at 30 minutes

patients suffered from bradycardia or oxygen desaturation. Tachycardia was observed in one patient from Group P and in two patients from Group K.

Discussion

Postoperative shivering is very unpleasant and physiologically stressful.¹ Studies have identified a host of different precipitating factors, including the male sex, the duration of the anaesthetic, spontaneous breathing techniques, use of volatile agents and anticholinergic medications.¹⁶ Unfortunately, except in some isolated cases, temperature monitoring and measures that are instituted to lessen the changes in core temperature during the perioperative period have not yet become standard practice.¹

Various nonpharmacological methods have been used to prevent body heat loss, such as heaters, forced-air warmers, blankets, radiant heating of the operating room and warming IV fluids.¹⁷ Potent anti-shivering properties have been attributed to numerous drugs.^{12,18,19} Pethidine is one of the most effective of these drugs. Although the mechanism of

action is not completely understood, it probably acts directly on the thermoregulatory centre or via opioid receptors.²⁰ It is likely that pethidine acts via κ receptors, rather than μ -opioid receptors, as the anti-shivering action of pethidine is inhibited by high-dose naloxone, which blocks μ and κ receptors, but not by low-dose naloxone, which blocks μ receptors only.¹⁴ Ketamine is a competitive receptor antagonist of N-methyl-D-aspartate (NMDA) receptors. It plays a role in thermoregulation at multiple levels. Neurons in the preoptic anterior horn hypothalamus in rats have been shown to increase their firing rate by application of NMDA. Furthermore, NMDA receptors modulate noradrenergic and serotonergic neurons in locus coeruleus.¹⁸ In addition to being a competitive NMDA receptor antagonist, ketamine has several other pharmacological properties. These include being a κ opioid agonist, blocking amine uptake in their descending inhibitory monoaminergic pain pathways, having a local anaesthetic action and interacting with muscarinic receptors. Therefore, it probably controls shivering by nonshivering thermogenesis, either by action on the hypothalamus or because of the β -adrenergic effect of norepinephrine.¹⁸ Studies have shown that a dose of 0.5 mg/kg ketamine is sufficient to prevent postoperative shivering.²⁰

Shivering was compared in the three groups at T0, and subsequently at T10, T20 and T30. The grades of shivering were found to be statistically more significant in the saline group than in the ketamine and pethidine groups. At T10, the saline group still experienced statistically more significant shivering than the other groups. However, the grades of shivering were comparable in the ketamine and pethidine groups. Similarly, at T20, shivering was again statistically greater in the saline group than in the other groups. On comparison, the grades of shivering between Group P and Group K were found to be statistically insignificant. At T30, the difference between the three groups was found to be statistically insignificant. The grades of shivering were comparable in all three groups after 30 minutes. The number of patients who shivered at T0 and subsequently at T10 and T20 was significantly less in Group P and Group K, than in Group S.

In our study, only one patient from Group K had hallucinations. The incidence of side-effects in all three groups was similar. Heart rate, mean arterial pressure and oxygenation were recorded at regular intervals, but no statistical difference was found between the groups. Ketamine causes sympathetic stimulation, but because of the low dose of ketamine that was used, it caused no statistically significant difference between the variables. Tympanic temperature was recorded intraoperatively and postoperatively. In any group, it was never less than 36°C and there was no need to warm any patient. The time to the first analgesic requirement in the saline group was shorter than that in Group P and Group

K. This could be because of the analgesic properties of ketamine at subanaesthetic doses and the analgesic nature of pethidine. Within the second postoperative hour, most patients in all three groups needed analgesia. This can be explained by the short duration of action of low-dose pethidine and ketamine.

In conclusion, all surgical patients should be kept normothermic unless hypothermia is specifically indicated. Anti-shivering prophylaxis is justified in patients who are at greater risk of developing postoperative shivering after general anaesthesia. Thus, prophylactic low-dose ketamine is as effective as pethidine in preventing postoperative shivering, without increasing the incidence of adverse reactions.

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