British Journal of Anaesthesia **95 (2)**: 189–92 (2005)
doi:10.1093/bja/aei148 Advance Access publication April 22, 2005

BJA

Efficacy of prophylactic ketamine in preventing postoperative shivering

D. Dal*, A. Kose, M. Honca, S. B. Akinci, E. Basgul and U. Aypar

Hacettepe University School of Medicine Department of Anaesthesiology and Reanimation, Ankara 06100, Turkey

**Corresponding author. E-mail: didemdal@yahoo.com*

Background. Treatment with ketamine and pethidine is effective in postoperative shivering. The aim of this study was to compare the efficacy of low-dose prophylactic ketamine with that of pethidine or placebo in preventing postoperative shivering.

Methods. A prospective randomized double-blind study involved 90 ASA I and II patients undergoing general anaesthesia. Patients were randomly allocated to receive normal saline (Group S, n=30), pethidine 20 mg (Group P, n=30) or ketamine 0.5 mg kg^{-1} (Group K, n=30) intravenously 20 min before completion of surgery. The anaesthesia was induced with propofol 2 mg kg^{-1}, fentanyl 1 μg kg^{-1} and vecuronium 0.1 mg kg^{-1}. It was maintained with sevoflurane 2–4% and nitrous oxide 60% in oxygen. Tympanic temperature was measured immediately after induction of anaesthesia, 30 min after induction and before administration of the study drug. An investigator, blinded to the treatment group, graded postoperative shivering using a four-point scale and postoperative pain using a visual analogue scale (VAS) ranging between 0 and 10.

Results. The three groups did not differ significantly regarding patient characteristics. The number of patients shivering on arrival in the recovery room, and at 10 and 20 min after operation were significantly less in Groups P and K than in Group S. The time to first analgesic requirement in Group S was shorter than in either Group K or Group P (P<0.005). There was no difference between the three groups regarding VAS pain scores.

Conclusion. Prophylactic low-dose ketamine was found to be effective in preventing postoperative shivering.

Br J Anaesth 2005; **95**: 189–92

Keywords: anaesthetics, i.v., ketamine; analgesics, opioid, pethidine; complications, shivering

Accepted for publication: April 5, 2005

Postoperative shivering occurs in 5–65% of patients recovering from general anaesthesia[1] and in ~30% of volunteers undergoing epidural anaesthesia.[2] This may be normal thermoregulatory shivering in response to core hypothermia or may result from the release of cytokines by the surgical procedure. The core temperature usually decreases by 0.5–1.5°C in the first hour after induction of anaesthesia. All general anaesthetics markedly impair normal autonomic thermoregulatory control. However, non-thermoregulatory shivering may also occur in normothermic patients in response to certain anaesthetics or postoperative pain.[3]

Postoperative shivering is very unpleasant and physiologically stressful. It may also cause complications, especially in patients with coronary artery disease, because of associated increases in oxygen consumption (by 100–600%), cardiac output, carbon dioxide production, and circulating catecholamines, and a significant decrease in mixed venous oxygen saturation.[1 3 4] Moreover, an increase in intracranial and intraocular pressure, interference with monitoring of ECG and blood pressure, increased metabolic rate, and lactic acidosis have been described in shivering patients.[1 3 4]

Various drugs have been investigated for prevention or treatment of postoperative shivering, including pethidine, ketanserin, sufentanil, alfentanil, tramadol, physostigmine, urapidil, nefopam, doxapram and nalbuphine.[1 3 4–6] Among the pharmacological agents, pethidine has been shown to be one of the most effective treatments.[6 7] Although its mechanism of action is not completely understood, it probably acts directly on the thermoregulatory centre[5] or via opioid receptors.[8] It is likely that *N*-methyl-D-aspartate (NMDA) receptor antagonists also modulate thermoregulation at multiple levels.[8] Ketamine, which is a competitive NMDA receptor antagonist, has been shown to inhibit postoperative shivering in one report.[9]

There has been no study regarding the use of ketamine as a prophylaxis against postoperative shivering. The aim of this study was to compare the efficacy of low-dose prophylactic ketamine with prophylactic pethidine and placebo for prevention of postoperative shivering.

Methods

The study was approved by the local hospital ethics committee. A prospective randomized double-blind study was performed after receiving written informed consent from the patients. We studied 90 patients of both genders aged 18–65 yr. All patients were ASA I or II and were undergoing general anaesthesia for an anticipated duration of 60–180 min. Procedures which might require administration of blood or blood products and urological endoscopic operations were excluded. Patients with BMI>30 kg m^{-2} and those with a history of convulsions, multiple allergies, hypertension, coronary artery disease or other cardiorespiratory or neuromuscular pathology were also excluded.

The patients were randomly (envelope randomization) allocated to receive saline (Group S, n=30), pethidine 20 mg (Group P, n=30) or ketamine 0.5 mg kg^{-1} (Group K, n=30) intravenously 20 min before the end of the surgery. The treatment drugs were prepared, diluted to a volume of 2 ml and presented as coded syringes by an anaesthetist who was not involved in the management of patients.

The anaesthetic management of the patients was standardized. All patients were informed about the visual analogue scale (VAS) before the operation. Heart rate, non-invasive blood pressure and oxygen saturation were recorded before and during surgery. Tympanic temperature was measured before anaesthesia, immediately after induction of anaesthesia, 30 min after induction and before administration of the study drug (ketamine, pethidine or saline). We planned to exclude patients with tympanic temperature <35°C, and to actively warm those with tympanic temperatures between 35–36 and 36°C. The anaesthesia was induced with i.v. propofol 2 mg kg^{-1} and fentanyl 1 μg kg^{-1}, and vecuronium 0.1 mg kg^{-1} was given to facilitate orotracheal intubation. Anaesthesia was maintained with nitrous oxide 60% in oxygen and sevoflurane 2–4%. Repeat doses of vecuronium 0.03–0.05 mg kg^{-1} were given if required. Approximately 20 min before completion of surgery patients were randomly assigned to receive the study drug. Residual neuromuscular blockade was reversed using neostigmine 0.03 mg kg^{-1} and atropine 0.01 mg kg^{-1}. When the patient's respiratory effort was adequate and he or she responded to verbal commands, the trachea was extubated. The type and duration of anaesthesia and surgery were recorded.

In the recovery room, all patients were monitored, received oxygen via a facemask and were covered with a cotton blanket. An anaesthetist unaware of the study drug observed the patient for shivering, pain, nausea and vomiting. Heart rate, non-invasive blood pressure, oxygen saturation and tympanic temperature were measured and recorded on admission to the recovery room (T0), and 10 min (T10), 20 min (T20) and 30 min (T30) thereafter. The shivering was graded using a four-point scale (Table 1) at these time intervals. The pain was assessed using a 0–10 cm visual analogue scale (VAS), where 0=no pain and 10=worst pain imaginable; the assessments were made on admission to the recovery room (T0) and then at the first (T1) and second (T2) hours in the recovery room. Any possible side-effects of the study drugs (i.e. nausea, vomiting, hypotension, tachycardia, hypertension or hallucinations) were recorded. Patients with nausea or vomiting were treated with metoclopramide 10 mg i.v. Postoperative pain was treated with methamizole 1000 mg i.v. during the first 30 min and with pethidine 20 mg i.v. after 30 min for VAS>3. The shivering was treated with pethidine 20 mg i.v. if the shivering grade was ⩾2. The administration times and the amounts of drug given during the first 2 h after the operation were recorded.

Table 1 Classification of shivering

Grade	Clinical signs
0	No shivering
1	Mild fasciculations of face or neck
2	Visible tremor involving more than one muscle group
3	Gross muscular activity involving the entire body

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) Windows version 10.0. Mean differences between the three groups regarding age, weight and height were tested using analysis of variance (ANOVA). Pain scores were compared using the Kruskal–Wallis test. The χ^2 test was used to analyse the difference between gender, ASA class, the number of shivering patients, those who required analgesics and who had nausea and vomiting. A value of P<0.05 was taken as significant. Post hoc comparisons were performed using the Bonferroni correction of the significance level. Power analysis showed that a sample size of 30 per group would achieve 93% power in the χ^2 test with a significance level of 0.01 at group proportions of 0.6 and 0.1.

Results

The three groups were comparable regarding distribution of age, weight, height, gender, duration of anaesthesia, duration of operation and ASA class (Table 2). The haemodynamic parameters and the tympanic temperatures were also similar in the three groups. The tympanic temperatures of the patients were >36°C and active warming was not required.

The number of patients with postoperative shivering on arrival in the recovery room, and then 10 min and 20 min after arrival, were significantly less in Group P and Group K than in Group S (Table 3). There was no difference between Groups P and K (P>0.05). In group S, 18 patients shivered

Table 2 Patient characteristics of the three treatment groups. Data are given as mean (range), mean (SD) or absolute numbers

	Group S (n=30)	Group P (n=30)	Group K (n=30)
Age (yr)	43 (18–65)	45 (18–65)	45 (21–66)
Female/male	23/7	24/6	24/6
Weight (kg)	67 (6)	71 (10)	65 (9)
Height (cm)	164 (6)	164 (8)	162 (9)
ASA I/II	25/5	26/4	26/4

Table 3 Number of patients with different grades of shivering in the three treatment groups. T0, arrival in the recovery room; T10, 10 min after arrival; T20, 20 min after arrival; T30, 30 min after arrival. *P<0.01 between Group S and Group P; †P<0.01 between Group S and Group K

	Grade 0/1/2/3			P-value
	Group S	Group P	Group K	
T0	18/4/2/6	30/0/0/0*	30/0/0/0†	<0.001
T10	15/5/4/6	30/0/0/0*	29/1/0/0†	<0.001
T20	23/7/0/0	30/0/0/0*	28/1/1/0†	<0.008
T30	28/2/0/0	30/0/0/0	28/0/2/0	0.088

Table 4 Pain scores using Visual Analogue Scale (VAS) expressed as median (5th–95th percentile) in the three groups. VAS0, on arrival in the recovery room; VAS1, at first postoperative hour; VAS2, at second postoperative hour

	Group S	Group P	Group K	P-value
VAS0	6 (4–8)	6 (2–8)	5 (0–7)	0.85
VAS1	3 (1.5–6)	4 (1.5–6)	3.5 (1.5–6)	0.51
VAS2	2 (1–3)	3 (1–4)	3 (1.5–5)	0.05

at grade ⩾2 and were subsequently treated with pethidine 20 mg i.v. In Group K, three patients reached grade ⩾2. In Group P none of the patients reached grade ⩾2 (P<0.001). At 30 min after operation, there were no differences between the three groups (Table 3). None of the patients required a second dose of pethidine for a shivering grade ⩾2 within the 30-min period.

The time to first analgesic requirement in Group S (mean 12 [SD 9.5] min) was significantly shorter than that in Group K (25 [18] min) or Group P (32 [25] min) (P=0.01). Thirty minutes after operation, nine patients in Group S, 13 in Group P and 20 in Group K were treated with i.v. methamizole (P<0.01). More patients in group K needed methamizol than patients in Group S (P<0.01 between the two groups). After the 30-min period, within the first postoperative hour, 20 patients in Group S, 15 in Group P and 14 in Group K had VAS scores >3 and they were treated with i.v. pethidine (P>0.05). There was no difference between the three groups regarding VAS scores (Table 4). Three patients in Group S and seven each in Groups K and P had VAS scores >3 and were treated with i.v. pethidine in the second postoperative hour (P>0.05).

Three patients in Group S, one in Group K and five in Group P had nausea and vomiting (P>0.05). None of the patients had episodes of oxygen desaturation or respiratory depression during the study. No hallucinations, tachycardia, hypotension, hypertension or nystagmus were seen in any of the patients.

Discussion

Various drugs have been used to treat or prevent postoperative shivering, but the ideal treatment has not yet been found. Pethidine has been shown to be one of the most effective treatments.[6 7] In our study, none of the patients shivered after prophylactic pethidine. A study using naloxone indicated that pethidine may act via κ rather than μ opioid receptors. The anti-shivering action of pethidine was inhibited by high-dose naloxone, which blocks μ and κ receptors, but not by low-dose naloxone which blocks μ receptors only.[6] A disadvantage of pethidine is that it can cause respiratory depression in the presence of previously administered opioids or anaesthetics. Nausea and vomiting are also important side-effects.

Ketamine, a competitive NMDA receptor antagonist, also inhibits postoperative shivering. It is likely that NMDA receptor antagonists modulate thermoregulation at a number of levels. In rats, neurones in the preoptic-anterior hypothalamus have been shown to increase their firing rate by application of NMDA. Furthermore, NMDA receptors modulate noradrenergic and serotoninergic neurones in the locus coeruleus. In the dorsal raphe nucleus, serotonin acts as a neuromodulator to enhance the effects of NMDA receptors. Finally, NMDA receptors at the dorsal horn of spinal cord modulate ascending nociceptive transmission. 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 the descending inhibitory monoaminergic pain pathways, having a local anaesthetic action and interacting with muscarinic receptors. Therefore it probably controls shivering by non-shivering thermogenesis either by action on the hypothalamus or by the β-adrenergic effect of norepinephrine.[8 9] In our study three patients still had grade ⩾2 shivering after ketamine prophylaxis and were treated with i.v. pethidine. Pethidine was effective in these three patients probably because pethidine and ketamine have different mechanisms of action. Another explanation could be that this dose of ketamine was not optimum. We chose a dose of 0.5 mg kg^{-1} because the only other report with ketamine had used this dose effectively to treat shivering in the postoperative period.[9] In that study, involving 30 patients for different types of surgery under spinal, epidural or general anaesthesia in which halothane was used as one of the anaesthetics, ketamine was reported to be quite useful in spinal and epidural anaesthesia, where it provided sedation and analgesia, but two patients developed hallucinations and four developed delirium.[9] Although none of our patients had hallucinations when ketamine was given ~20 min before

completion of surgery under general anaesthesia, this very well known side-effect of ketamine should always be kept in mind.

In this study, we found no difference between the efficacy of ketamine and pethidine in preventing postanaesthetic shivering. As far as we are aware, this study is the first in which ketamine has been used prophylactically. Postoperative shivering is a common phenomenon, and in our placebo group the incidence was 60%, a proportion that is similar to that reported in other studies.[1] It has been attributed to a number of factors, including uninhibited spinal reflexes, pain, decreased sympathetic activity, adrenal suppression, release of pyrogenic mediators during surgery, administration of volatile anaesthetics, opiate withdrawal, blood loss, duration of surgery and thermoregulatory shivering in response to hypothermia.[4 5 10] However, no relationship has been shown between axillary temperature and occurrence of shivering.[5] Postoperative shivering can be treated by skin surface warming, radiant heat application or pharmacological agents.[5] In our study there were no significant differences in tympanic temperature among the groups. The tympanic temperatures of the patients were >36°C and there was no need for active warming.

In the postoperative period, the time to first analgesic requirement in the placebo group (12 [9.5] min) was shorter than that in the ketamine group (25 [18] min) or the pethidine group (32 [25] min). In the first 2 h after operation, all the patients in the three groups needed analgesics (methamizole or pethidine). This can be explained by the short duration of action of low-dose pethidine (20 mg) and ketamine (0.5 mg kg^{-1}). Although there are not enough data to draw firm conclusions about methamizole, both methamizole and pethidine suppress postanaesthetic shivering.[11 12] Methamizole given for pain relief in the first 30 min might have augmented the antishivering effects of ketamine or pethidine. On the other hand, administration of pethidine as a rescue medication for shivering in the first 30 min might also have influenced the results in the opposite way.

One of the disadvantages of pethidine is its interaction with previously administered opioids or anaesthetics, leading to respiratory depression. Nausea and vomiting are also important side-effects. Although our study did not have sufficient power to show any difference between the two drugs, ketamine may have at least theoretical advantages over pethidine regarding respiratory depression, nausea and vomiting. For these reasons ketamine can be an alternative prophylaxis against postoperative shivering in patients with bradycardia, hypotension, respiratory depression, nausea, vomiting and allergic reactions to pethidine. Future studies may find the optimal dose of ketamine for this purpose.

References

1 Singh P, Dimitriou V, Mahajan RP, Crossley AWA. Double-blind comparison between doxapram and pethidine in the treatment of postanaesthetic shivering. *Br J Anaesth* 1993; **71:** 685–8

2 Horn EP, Werner C, Sessler DI, Steinfath M, Schulte am Esch J. Late intraoperative clonidine administration prevents postanesthetic shivering after total intravenous or volatile anesthesia. *Anesth Analg* 1997; **84:** 613–17

3 Mathews S, Al Mulla A, Varghese PK, Radim K, Mumtaz S. Postanaesthetic shivering–a new look at tramadol. *Anaesthesia* 2002; **57:** 394–8

4 Piper SN, Suttner SW, Schmidt CC, Maleck WH, Kumle B, Boldt J. Nefopam and clonidine in the prevention of postanaesthetic shivering. *Anaesthesia* 1999; **54:** 695–9

5 Vanderstappen I, Vandermeerch E, Vanacker B, Mattheussen M, Herijgers P, Van Aken H. The effect of prophylactic clonidine on postoperative shivering: a large prospective double-blind study. *Anaesthesia* 1996; **51:** 351–5

6 Wrench IJ, Cavill G, Ward JEH, Crossley AWA. Comparison between alfentanil, pethidine and placebo in the treatment of post-anaesthetic shivering. *Br J Anaesth* 1997; **79:** 541–2

7 Terasako K, Yamamoto M. Comparison between pentazocine, pethidine and placebo in the treatment of post-anaesthetic shivering. *Acta Anaesthesiol Scand* 2000; **44:** 311–2

8 De Witte J, Sessler DI. Perioperative shivering: physiology and pharmacology. *Anesthesiology* 2002; **96:** 467–84

9 Sharma DR, Thakur JR. Ketamine and shivering. *Anaesthesia* 1990; **45:** 252–3

10 Sessler DI, Israel D, Pozos RS, Pozos M, Rubinstein EH. Spontaneous post-anesthetic tremor does not resemble thermoregulatory shivering. *Anesthesiology* 1988; **68:** 843–50

11 Monso A, Riudeubas J, Barbal F, Laporte JR, Arnau JM. A randomized, double-blind, placebo-controlled trial comparing pethidine to metamizol for treatment of post-anaesthetic shivering. *Br J Clin Pharmacol* 1996; **42:** 307–11

12 Kranke P, Eberhart LH, Roewe N, Tramer MR. Pharmacological treatment of postoperative shivering: A quantitative systematic review of randomized controlled trials. *Anesth Analg* 2002; **94:** 453–60