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Comparison of prophylactic use of midazolam, ketamine, and ketamine plus midazolam for prevention of shivering during regional anaesthesia: a randomized double-blind placebo controlled trial

A. Honarmand* and M. R. Safavi

Department of Anesthesiology and Intensive Care, Isfahan University of Medical Sciences, Isfahan, Iran
Corresponding author. E-mail: honarmand@med.mui.ac.ir

Background. Regional anaesthesia, like general anaesthesia, influences the thermoregulatory process. The aim of the present study was to compare the efficacy of low-dose prophylactic midazolam with that of placebo, ketamine, and a combination of ketamine and midazolam in the prevention of shivering caused by regional anaesthesia.

Methods. In this double-blind study, 120 ASA I and II patients undergoing orthopaedic surgery were included. Subarachnoid anaesthesia was performed in all patients with bupivacaine 15 mg. The patients were randomly allocated to receive saline (Group C), ketamine 0.5 mg (Group K), midazolam 75 μg kg^{-1} (Group M), or ketamine 0.25 mg+midazolam 37.5 μg kg^{-1} (Group KM). During surgery, a shivering score was recorded at 5 min intervals. Tympanic and axillary temperature were recorded at 10 min intervals during the perioperative period.

Results. After 15 min, the incidences of shivering in Groups C, M, K, and KM were 60%, 50%, 23.3%, 3.3%, respectively ($P=0.000$). The differences between Group KM and Groups M, K, and C were statistically significant ($P=0.000$, $P=0.026$, $P<0.001$, respectively). The number of patients with a shivering score of ≥ 3 was significantly higher in Group C compared with Groups M, K, and KM (8 *vs* 4, 1, and 0, respectively, $P=0.040$).

Conclusions. Prophylactic use of ketamine 0.25 mg kg^{-1}+midazolam 37.5 μg kg^{-1} i.v. was more effective than ketamine 0.5 mg kg^{-1} i.v. or midazolam 75 μg kg^{-1} i.v. in preventing shivering developed during regional anaesthesia.

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Regional anaesthesia may impair thermoregulatory control[1] and up to a 57% incidence of shivering during regional anaesthesia has been reported.[2] Shivering during neuraxial anaesthesia could have potentially detrimental effects.[3]

Regional anaesthesia produces vasodilatation, which facilitates core-to-peripheral redistribution of heat.[4] Ketamine increases arterial pressure, heart rate, and cardiac output because of direct central sympathetic stimulation and inhibition of norepinephrine uptake into postganglionic sympathetic nerve endings, and may decrease core-to-peripheral redistribution of heat.[5] Thus, it may be logical to use ketamine in patients who are at risk of hypothermia.

Sagir and colleagues[6] showed that the prophylactic use of 0.5 mg kg^{-1} i.v. ketamine was effective in preventing shivering developed during regional anaesthesia, but patients may develop hallucinations and postoperative nausea or vomiting.

Among benzodiazepines, diazepam has been found to be effective in the prevention of postoperative shivering.[7] Midazolam, even in plasma concentrations far exceeding those used routinely, produces minimal impairment of thermoregulatory control.[8] Kurz and colleagues[8] studied the effect of midazolam on thermoregulation and found that reduction in heat production after administration of midazolam is less than that after induction of anaesthesia with clinical doses of volatile anaesthetics, propofol, and opioids.

To the best of our knowledge, there is no study regarding the use of midazolam or a midazolam–ketamine

combination as a prophylactic agent against intra- or postoperative shivering during regional anaesthesia. Also, there is no study comparing prophylactic use of midazolam or midazolam–ketamine combination with ketamine to prevent shivering developed during regional anaesthesia.

This prospective, randomized, double-blind, placebo controlled study was performed to compare i.v. midazolam, midazolam and ketamine in combination, i.v. ketamine, and placebo (saline) for the prevention of shivering in patients who underwent elective surgery under regional anaesthesia.

Methods

After obtaining institutional approval and written informed consent from all patients, 120 ASA I and II patients between the ages of 18–60 yr who were undergoing elective orthopaedic surgery under spinal anaesthesia were enrolled in the study. Patients with hypo- or hyperthyroidism, cardiopulmonary disease, psychological disorders, a need for blood transfusion during surgery, an initial body temperature $>38.0°C$ or $<36°C$, a known history of alcohol or substance abuse, or receiving vasodilators, or medications likely to alter thermoregulation were excluded from the study.

Patients did not receive premedication. On arrival in the operating theatre, all patients had a venous cannula inserted. I.V. fluids were preheated to 37°C in a warmed cabinet and given without in-line warming. No other warming device was used. Lactated Ringer's solution warmed to 37°C was infused at 10 ml kg^{-1} h^{-1} over 30 min before spinal anaesthesia. The infusion rate was then reduced to 6 ml kg^{-1} h^{-1}.

Heart rate, mean arterial pressure (MAP), and peripheral oxygen saturation were recorded using standard non-invasive monitors before intrathecal injection and thereafter at 5, 10, 15, 20, 25, and 30 min. Before intrathecal injection and 10 min intervals during the perioperative period, body temperatures (tympanic and axillary temperature) were recorded with an ear thermometer (OMRON Medizintechnik GmbH, Mannheim, Germany) and an axillary thermometer. The ambient temperature was measured by a wall thermometer. The ambient temperature was maintained at 24°C with constant humidity.

Subarachnoid anaesthesia was instituted at either L3/4 or L4/5 interspaces. Isobaric bupivacaine, 5 mg ml^{-1}, 15 mg was injected using a 22 G Quincke spinal needle. The patients were randomly (envelope randomization) allocated to receive saline (Group P, $n=30$), ketamine 0.5 mg kg^{-1} (Group K, $n=30$), midazolam 75 μg kg^{-1} (Group M, $n=30$), or ketamine 0.25 mg kg^{-1} and midazolam 37.5 μg kg^{-1} (Group KM, $n=30$). Just after intrathecal injection, all drugs were given as an i.v. bolus. The treatment drugs were diluted to a volume of 4 ml and presented as coded syringes by an anaesthesiologist who was blinded to the group allocation. Supplemental oxygen (5 litre min^{-1}) was delivered via a facemask during the operation. All patients were covered with one layer of surgical drapes over the chest, thighs, and calves during the operation and one cotton blanket over the entire body after operation.

During the preoperative period, sensory block was assessed with a pinprick test at 5 min intervals. The presence of shivering was observed by an observer blinded to the study drug administered. Shivering was graded using a scale similar to that validated by Tsai and Chu:[9] 0, no shivering; 1, piloerection or peripheral vasoconstriction but no visible shivering; 2, muscular activity in only one muscle group; 3, muscular activity in more than one muscle group but not generalized; and 4, shivering involving the whole body. During surgery, a shivering score was recorded at 5 min intervals. If 15 min after spinal anaesthesia and concomitant administration of a prophylactic dose of one of the study drugs, Grade 3 or 4 shivering was noted, the prophylaxis was regarded as ineffective and i.v. meperidine 25 mg was administered.

Side-effects, such as hypotension, nausea and vomiting, and hallucinations, were recorded. Hypotension was defined as a decrease in MAP of more than 20% from baseline (baseline MAP was calculated from three measurements taken on the ward before surgery). This was treated by crystalloid infusion and if necessary ephedrine 5 mg was administered i.v. The amount of ephedrine given in each group was recorded. If patients developed nausea and vomiting, i.v. metoclopramide 10 mg was administered. Hallucination as a side-effect was defined as a false sensory experience where the patients reported they saw, heard, smelled, tasted, and felt something that was non-existent.

The attending anaesthetist also assessed the degree of sedation on a five-point scale: 1, fully awake and oriented; 2, drowsy; 3, eyes closed but rousable to command; 4, eyes closed but rousable to mild physical stimulation; and 5, eyes closed but unrousable to mild physical stimulation.[10]

Statistical analysis

Previous studies have found an incidence of shivering of the order of 40–65%. We anticipated an incidence of 45% in the control group and took a difference of 40% in the incidence of shivering between control and treated groups as being clinically meaningful. Hence, we calculated that 30 patients were required in each group for a type I error of 0.05 and a type II error of 0.2. Statistical analysis was performed using the SPSS statistical package (version 14.0; SPSS Inc., Chicago, IL, USA). Continuous variables, including haemodynamic data and temperature values over time within the groups, were analysed using repeated measures analysis of variance (ANOVA) followed by Bonferroni's *post hoc* testing. Statistical comparisons among the groups were performed using two-way ANOVA, followed by unpaired *t*-tests with Bonferroni's correction.

Nominal or categorical data including the overall incidence of shivering between the four groups were analysed and compared using the χ^2 test. Fisher's exact test was used when fewer than five patients were expected. Sedation score between the four groups was compared using the Kruskal–Wallis test. Values are given as mean (SD) or median (range). $P<0.05$ was considered statistically significant.

Results

One hundred and twenty-five patients were approached for the study. Two patients were excluded due to psychological disorder and three patients due to cardiopulmonary disease. Patient characteristics including sex, duration of surgery, and the median level of sensory block were similar among the groups (Table 1). In Group KM, after spinal anaesthesia and concomitant administration of a prophylactic dose of the study drug, shivering after 15 min was observed only in one patient and it was significantly different when compared with Groups M (15/30), K (7/30), and C (18/30) ($P=0.000$, $P=0.026$, $P=0.000$, respectively) (Tables 1 and 2).

After 15 min of spinal analgesia, Grade 4 shivering was observed in one patient in Group M and in one patient in Group C. Thirty-seven per cent of the patients (11/120) experienced Grade 3 shivering and requested treatment. In Group C, eight out of 30 patients experienced shivering at Grade ≥ 3. This was significantly higher than Groups K and KM ($P=0.026$, $P=011$, respectively). These patients were subsequently treated with i.v. meperidine 25 mg. After the first dose of meperidine, shivering ceased in all patients.

The sedation score was 1 in all patients just after intrathecal injection and before given treatment drugs. However, 15 min after spinal anaesthesia, the median (range) sedation score was significantly higher in Group M 2 (1–4) than Groups KM 1 (1–3) ($P=0.001$) and C 1 (1–3) ($P=0.000$) and was higher in Group K 2 (1–3) than in Group C ($P=0.001$) using the Kruskal–Wallis test. Sedation score was not significantly different between Group KM and Group C ($P=0.133$). Using repeated measures ANOVA followed by Bonferroni's *post hoc* testing, MAP and heart rate values were not significantly different between the groups at any time during the study.

Data on episodes of hypotension are reported in Table 3. In these patients, ephedrine 10 mg was successful in the treatment of hypotension. After 30 min, haemodynamic measurements were stable and were not compared. Incidence of hallucination and nausea and vomiting was not significantly different between the four groups (Table 3).

The axillary body temperatures increased significantly from the 10th to 80th min interval in Groups M, K, and KM when compared with the baseline ($P<0.05$). Using ANOVA followed by Bonferroni's *post hoc* testing, the axillary body temperatures in Group KM were significantly higher than in the other groups in the 10th–80th min ($P<0.044$) (Fig. 1).

The decreases in core temperatures were statistically significant in Groups M, K, and C when compared with the baseline level ($P<0.05$). Using ANOVA followed by Bonferroni's *post hoc* testing, the core temperature decreases seen in Group KM were significantly less than the other groups beginning from the 10th min ($P<0.025$) (Fig. 2). The core temperature change in Group M was not statistically different from Group C.

Discussion

In this study, it was shown that prophylactic use of ketamine 0.25 mg kg^{-1} and midazolam 37.5 µg kg^{-1} i.v. is better than ketamine 0.5 mg kg^{-1} i.v. or midazolam 75 µg kg^{-1} i.v. in preventing shivering related to regional anaesthesia.

Sagir and colleagues[6] compared placebo, ketamine, granisetron, and a combination of ketamine and granisetron for the prevention of shivering caused by regional anaesthesia, and found that the incidence of shivering was 55% (22/40) in the control group. In another study to determine whether meperidine (0.2 mg kg^{-1}), added to bupivacaine and a morphine spinal mixture, decreases the incidence and intensity of shivering during spinal anaesthesia for Caesarean delivery, the incidence of shivering

Table 1 Patients characteristics, duration of surgery, median level of sensory block, and incidence of shivering in the four groups. Data are presented as mean (SD), median (range), or number (%) of patients. Ages are presented as mean (range). The median level of sensory block was similar in the four groups. Shivering refers to any shivering, i.e. Grades 1–4. *$P<0.001$; †$P=0.000$ *vs* Group M or Group C; ‡$P=0.026$ *vs* Group K

	Group M	Group K	Group KM	Group C
Number of patients	30	30	30	30
Age (yr)	38.7 (20–65)	39.8 (28–65)	40.8 (22–65)	41.7 (22–65)
Gender (F/M)	8/22	10/20	12/18	11/19
Weight (kg)	66.7 (11.1)	67.9 (9.8)	68.4 (13.7)	64.9 (12.2)
Height (cm)	166.4 (9.1)	169.0 (10.7)	169.2 (10.8)	167.5 (12.1)
ASA (I/II)	24/6	26/4	27/3	25/5
Duration of surgery (min)	80.3 (13.7)	78.0 (12.5)	79.9 (12.9)	81.7 (13.0)
Median level of sensory block (dermatome)	T8 (T6–T10)	T8 (T4–T9)	T8 (T6–T10)	T8 (T4–T10)
Shivering n (%)*	15 (50)	7 (23.3)	1 (3.3)†,‡	18 (60)

Table 2 Number (%) of patients with different grades of shivering after 15 min of spinal analgesia. *P<0.001 vs Group M or Group C. †P=0.026 vs Group K

Shivering score	Group M (n=30)	Group K (n=30)	Group KM (n=30)	Group C (n=30)
0	15 (50.0)	23 (76.7)	29 (96.7)*·†	12 (40.0)
1	9 (30.0)	4 (13.3)	0 (0.0)	7 (23.3)
2	2 (6.70)	2 (6.7)	1 (3.3)	3 (10.0)
3	3 (10.0)	1 (3.3)	0 (0.0)	7 (23.3)
4	1 (3.30)	0 (0.0)	0 (0.0)	1 (3.30)

during surgery was reported to be 85%.[11] Kelsaka and colleagues[12] compared the efficacy of ondansetron and meperidine in the prevention of shivering during and after spinal anaesthesia. They reported that shivering was observed in 8% of the ondansetron group, 8% of the meperidine group, and 36% of the control group. In our study, the incidence of shivering was 60% (18/30) in the control group. The lower incidence of shivering in Kelsaka's study was probably due to a number of reasons: first, in contrast to our study, all patients in Kelsaka's study received 10 mg diazepam orally for premedication 45 min before surgery. Secondly, in Kelsaka's study, shivering was evaluated by observing the pectoralis major muscles for fasciculations for more than 10 s. In our study, shivering was graded using a scale similar to that validated by Tsai and Chu,[9] which considered piloerection or peripheral vasoconstriction, but no visible shivering as Grade 1.

Hypothermia during regional anaesthesia is common[13] and can be nearly as severe as that observed during general anaesthesia.[14] There are three principal reasons for hypothermia under spinal anaesthesia. First, spinal anaesthesia leads to an internal redistribution of heat from the core to the peripheral compartment.[15] Secondly, with loss of thermoregulatory vasoconstriction below the level of the spinal block, there is increased heat loss from body surfaces. Lastly, there is altered thermoregulation under spinal anaesthesia characterized by a 0.5°C decrease in vasoconstriction and shivering thresholds.[1]

Various pharmacological treatments including i.v. administration of the opioids meperidine, alfentanil, and nalbuphine;[16][17] the non-opioid analgesic tramadol,[18] ondansetron, dolasetron; the 5-HT3 antagonists;[19][20] and the cholinomimetic agent physostigmine[21] for postanaesthetic shivering have been used; however, side-effects

Table 3 Incidence of hypotension, nausea and vomiting, and hallucination among the four groups

	Group M (n=30)	Group K (n=30)	Group KM (n=30)	Group C (n=30)	P-value
Hypotension	5 (16.6%)	3 (10.0%)	4 (13.3%)	7 (23.3%)	0.534
Nausea and vomiting	3 (10.0%)	9 (30.0%)	8 (26.0%)	8 (26.0%)	0.251
Hallucination	0 (0.0%)	3 (10.0%)	2 (6.7%)	0 (0.0%)	0.131

of these agents include hypotension, hypertension, sedation, respiratory depression, and nausea and vomiting.[16][17]

Goold and colleagues[22] have shown that diazepam premedication prevents postoperative shivering. Grover and colleagues[23] showed that administration of midazolam 0.03 µg kg^{-1} i.v. towards the end of the anaesthetic procedure hastens the gain of core temperature and shivering subsides earlier in the postoperative period in patients undergoing brachytherapy for carcinoma or the cervix. Kurz and colleagues[8] showed that, in contrast to low-dose propofol[24] and opioids, midazolam does not produce substantial inhibition of thermoregulation. This explains the lower incidence of shivering observed in our patients receiving midazolam.

GABA receptors have been demonstrated in the spinal cord. GABAergic neurones mediate presynaptic inhibition, suppressing signals from muscle and cutaneous receptors. Benzodiazepines have been found to reduce repetitive firing in response to depolarizing pulses in mouse spinal cord neurones.[25] Such inhibitory functions of midazolam in the spinal cord may be responsible for inhibiting the conduction of afferent impulses from muscle spindles and cutaneous receptors for cold to the higher centres, thereby and so suppressing shivering.

Ketamine, which is a competitive receptor antagonist of N-methyl-D-aspartic acid (NMDA), has a role in thermoregulation at various levels. In rats, application of NMDA agonist increases the firing rate of neurones in the preoptic-anterior hypothalamus. Moreover, NMDA receptors act by modulating the noradrenergic and serotoninergic neurones in the locus ceroleus. Serotonin, as a neuromodulator, enhances the effects of the NMDA receptor in the dorsal raphe nucleus. Finally, NMDA receptors modulate ascending nociceptive transmission at the dorsal horn of the spinal cord.[26] Additionally, ketamine has many other pharmacological properties such as blocking amine uptake in the descending inhibitory monoaminergic pain pathways, interacting with muscarinic receptors, having a local anaesthetic action, and being a K opioid agonist. Ketamine probably controls shivering by nonshivering thermogenesis either by action on the hypothalamus or by the b-adrenergic effect of norepinephrine.[27]
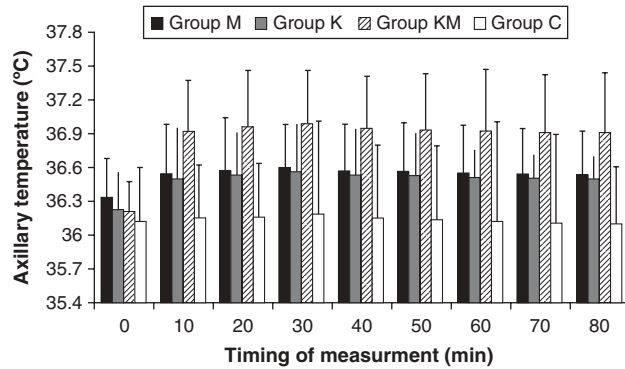
Ketamine causes sympathetic stimulation and vasoconstriction in patients at risk of hypothermia. This effect of ketamine is in contrast to that of midazolam which reduces core-body temperature by inhibiting tonic thermoregulatory vasoconstriction.[23]

Kinoshita and colleagues[28] showed that during spinal anaesthesia, infusion of low-dose ketamine prevents decreases in the body temperature of patients sedated with propofol. Ketamine has been shown to prevent shivering without producing haemodynamic alterations in patients undergoing regional anaesthesia.[27] These data are consistent with the antishivering effects of premedication with ketamine observed in the present study without significant haemodynamic changes.
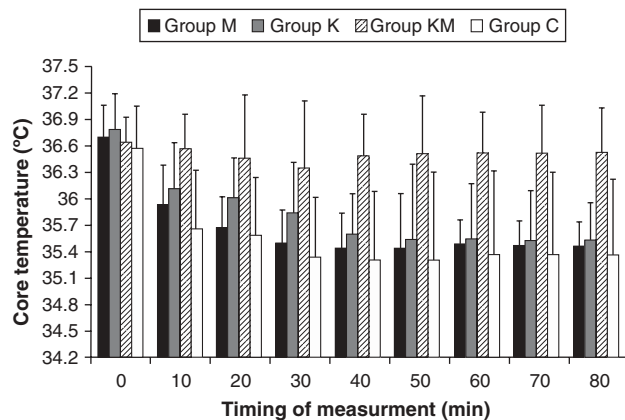
Fig 1 Change in peripheral temperature with time. Data are presented as mean (SD). There was significant difference between the groups by using repeated measures ANOVA followed by Bonferroni's *post hoc* testing ($P=0.001$). Axillary temperatures significantly increased in the 10th–80th min interval in Groups M, K, and KM when compared with the baseline level ($P<0.05$). Using ANOVA followed by Bonferroni's *post hoc* testing: $P<0.044$ for the comparison of Group KM with the other groups and $P<0.025$ for the comparison between Group C with Groups K and M. For clarity, significance on *post hoc* testing is not indicated.

It is clear from our data that the combination of ketamine and midazolam prevents the hypothermia that is often seen with premedication with midazolam alone. It is probable that ketamine prevented the arteriovenous shunt vasodilation normally induced by midazolam. Since these shunts are under sympathetic control,[29] it seems plausible that ketamine acts centrally to inhibit the effect of midazolam.

In summary, i.v. midazolam premedication reduces core-body temperature by inhibiting tonic thermoregulatory

vasoconstriction. In contrast, ketamine premedication increased core temperature. Core temperature remained unchanged when the two drugs were combined, suggesting that the thermoregulatory effects of a benzodiazepine receptor agonist and competitive receptor antagonist of NMDA oppose each other. Further clinical trials are needed to confirm the benefits of combining ketamine and midazolam to prevent shivering.

References

1 Ozaki M, Kurz A, Sessler DI, *et al.* Thermoregulatory thresholds during spinal and epidural anesthesia. *Anesthesiology* 1994; **81**: 282–8

2 Jeon YT, Jeon YS, Kim YC, Bahk JH, Do SH, Lim YJ. Intrathecal clonidine does not reduce post-spinal shivering. *Acta Anaesthesiol Scand* 2005; **49**: 1509–13

3 Ciofolo MJ, Clergue F, Devilliers C, Ben-Ammar M, Viars P. Changes in ventilation, oxygen uptake, and carbon dioxide output during recovery from isoflurane anesthesia. *Anesthesiology* 1989; **70**: 737–41

4 Glosten B, Hynson J, Sessler DI, McGuire J. Preanesthetic skin-surface warming reduces redistribution hypothermia caused by epidural block. *Anesth Analg* 1993; **77**: 488–93

5 Ikeda T, Kazama T, Sessler DI, *et al.* Induction of anesthesia with ketamine reduces the magnitude of redistribution hypothermia. *Anesth Analg* 2001; **93**: 934–8

6 Sagir O, Gulhas N, Toprak H, Yucel A, Begec Z, Ersoy O. Control of shivering during regional anaesthesia: prophylactic ketamine and granisetron. *Acta Anaesthesiol Scand* 2007; **51**: 44–9

7 Hopkin DA. Postoperative spasticity and shivering. *Anaesthesia* 1984; **39**: 725–6

8 Kurz A, Sessler DI, Annadata R, Dechert M, Christensen R, Bjorksten AR. Midazolam minimally impairs thermoregulatory control. *Anesth Analg* 1995; **81**: 393–8

9 Tsai YC, Chu KS. A comparison of tramadol, amitriptyline, and meperidine for postepidural anesthetic shivering in parturients. *Anesth Analg* 2001; **93**: 1288–92

10 Wilson E, David A, MacKenzie N, Grant IS. Sedation during spinal anaesthesia: comparison of propofol and midazolam. *Br J Anaesth* 1990; **64**: 48–52

11 Roy JD, Girard M, Drolet P. Intrathecal meperidine decreases shivering during cesarean delivery under spinal anesthesia. *Anesth Analg* 2004; **98**: 230–4

12 Kelsaka E, Baris S, Karakaya D, Sarıhasan B. Comparison of ondansetron and meperidine for prevention of shivering in patients undergoing spinal anesthesia. *Reg Anesth Pain Med* 2006; **1**: 40–5

13 Hendolin H, Lansimies E. Skin and central temperatures during continuous epidural analgesia and general anaesthesia in patients subjected to open prostatectomy. *Ann Clin Res* 1982; **14**: 181–6

14 Frank SM, Beattie C, Christopherson R, *et al.* Epidural versus general anesthesia, ambient operating room temperature, and patient age as predictors of inadvertent hypothermia. *Anesthesiology* 1992; **77**: 252–7

15 Matsukawa T, Sessler DI, Christensen R, *et al.* Heat flow and distribution during epidural anesthesia. *Anesthesiology* 1995; **83**: 961–7

16 Wrench IJ, Cavill G, Ward JE, Crossley AWA. Comparison between alfentanil, pethidine and placebo in the treatment of postanaesthetic shivering. *Br J Anaesth* 1997; **79**: 541–2

Fig 2 Change in core temperature with time. Data are presented as mean (SD). There was significant difference between the groups by using repeated measures ANOVA followed by Bonferroni's *post hoc* testing ($P<0.0010$). The decreases in core temperatures were statistically significant in Groups M, K, and C when compared with the baseline level ($P<0.05$). For clarity, these are not shown. By using ANOVA followed by Bonferroni's *post hoc* testing: $P<0.020$ for the comparison of Group KM compared with the other groups and $P<0.025$ for the comparison between Group C with Group K. There was no significant difference in core temperature between Group M and Group C. For clarity, significance on *post hoc* testing is not indicated.

17 Wang JJ, Ho ST, Chun S, Liu YC. A comparison among nalbu-phine, meperidine and placebo for treating postanesthetic shivering. *Anesth Analg* 1999; **88**: 686–9

18 DeWitte J, Deloof T, DeVeylder J, Housmans PR. Tramadol in the treatment of postanesthetic shivering. *Acta Anaesthesiol Scand* 1997; **41**: 506–10

19 Powell R, Buggy D. Ondansetron given before induction of anesthesia reduces shivering after general anesthesia. *Anesth Analg* 2000; **90**: 1423–7

20 Bock M, Sinner B, Göttlicher M, Simon E, Martin E, Motsch J. Involvement of serotonergic pathways in postanaesthetic cold defence: dolasetron prevents shivering. *J Therm Biol* 2002; **27**: 159–66

21 Horn EP, Standl T, Sessler DI, *et al.* Physostigmine prevents post-anesthetic shivering as does meperidine or clonidine. *Anesthesiology* 1998; **88**: 108–13

22 Goold JE. Postoperative spasticity and shivering. A review with personal observations of 500 patients. *Anaesthesia* 1984; **39**: 35–8

23 Grover VK, Mahajan R, Yaddanapudi LN, Sudarshana HG, Gill KD. Efficacy of midazolam in preventing postoperative shivering. *Int J Clin Pharmacol Ther* 2002; **40**: 534–6

24 Leslie K, Sessler DI, Bjorksten A, *et al.* Propofol causes a dose-dependent decrease in the thermoregulatory threshold for vaso-constriction, but has little effect on sweating. *Anesthesiology* 1994; **81**: 353–60

25 Adam RD, Victor M, Ropper AH. Motor paralysis. In: Adam RD, Victor M, Ropper AH, eds. *Principles of Neurology,* 6th Edn. New York: McGraw Hill Inc., 1997; 45–63

26 Dal D, Kose A, Honca M, Akinci B, Basgul E, Aypar U. Efficacy of prophylactic ketamine in preventing postoperative shivering. *Br J Anaesth* 2005; **95**: 189–92

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

28 Kinoshita T, Suzuki M, Shimada Y, Ogawa R. Effect of low-dose ketamine on redistribution hypothermia during spinal anesthesia sedated by propofol. *J Nippon Med Sch* 2004; **71**: 92–8

29 Hales JRS. Skin arteriovenous anastomoses, their control and role in thermoregulation. In: Johansen K, Burggren W, eds. *Cardiovascular Shunts: Phylogenetic, Ontogenetic and Clinical Aspects.* Copenhagen, Denmark: Munksgaard, 1985; 433–51