

## Effectiveness of low-dose midazolam plus ketamine in the prevention of shivering during spinal anaesthesia for emergency lower limb surgery

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### Abstract

**Objective:** This study was conducted to compare the effectiveness of two different dosages of intravenous midazolam in combination with ketamine in the prevention of shivering during spinal anaesthesia for emergency lower limb surgery.

**Design:** This was a prospective, randomised, double-blind, placebo-controlled study.

**Setting and subjects:** We studied 90 patients with American Society of Anesthesiologists classification I and II, aged between 18 and 60 years old, and randomly allocated to receive either a combination of low-dose midazolam 0.02 mg/kg plus ketamine 0.25 mg/kg (Group A), or a combination of higher-dose midazolam 0.04 mg/kg plus ketamine 0.25 mg/kg (Group B), or normal saline as the control group (Group C), after an intrathecal injection of 0.5% hyperbaric bupivacaine 12.5-15 mg.

**Outcome measures:** The outcomes measured were the incidence and the degree of shivering, the effectiveness and the side-effects of two different dosages of the drugs in preventing shivering.

**Results:** In this study, the incidence of shivering was 46% in Group C, which was significantly higher than that in Group A (16%) and Group B (10%) ( $p$ -value  $< 0.05$ ). However, there was no difference between Group A and B ( $p$ -value = 0.704). The number of patients with shivering grade  $\geq 2$  was significantly higher in Group C than it was in Groups A and B ( $p$ -value  $< 0.05$ ), but not between Group A and Group B. It was also found that there was no difference in the haemodynamic parameters in all three groups. However, patients in Groups A and B were more sedated ( $p$ -value  $< 0.05$ ), and had higher incidence of nystagmus than those in Group C ( $p$ -value  $< 0.001$ ).

**Conclusion:** Low-dose midazolam 0.02 mg/kg plus ketamine 0.25 mg/kg was equally effective when compared with a higher dose of midazolam 0.04 mg/kg plus ketamine 0.25 mg/kg in preventing shivering during spinal anaesthesia for emergency lower limb surgery. There were no significant changes in the haemodynamic parameters in all three groups. However, patients in the midazolam plus ketamine groups were more sedated and had a higher incidence of nystagmus.

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### Introduction

Regional anaesthesia may impair thermoregulatory control.<sup>1</sup> Shivering during regional anaesthesia is a common problem. An incidence of up to 55% shivering has been reported during regional anaesthesia.<sup>2</sup> Regional anaesthesia produces vasodilatation which facilitates core to peripheral redistribution of heat.<sup>3</sup>

Intraoperative shivering is very unpleasant and can be physiologically stressful. It may also cause complications,

especially in patients with coronary artery disease. It is associated with increased oxygen consumption, cardiac output and carbon dioxide production.<sup>4-6</sup> An increase in intraocular pressure and interference with monitoring of pulse oximeters has also been described.<sup>7,8</sup>

Pethidine has been shown to be one of the most effective treatments for post-anaesthetic shivering. However, it increases the risk of respiratory depression in the presence of previously administered parenteral or neuraxial opioids.

Nausea and vomiting are also important encountered side-effects with pethidine.<sup>9</sup>

Theoretically, ketamine has an advantage over pethidine as it does not cause respiratory depression. For this reason, ketamine is used as prophylaxis against postoperative shivering in patients with bradycardia, hypotension, respiratory depression and those with allergic reactions to pethidine. Ketamine causes direct central sympathetic stimulation and inhibition of norepinephrine uptake into the postganglionic sympathetic nerve endings. It decreases core to peripheral redistribution of heat.<sup>10</sup> Dal et al showed that the prophylactic use of 0.05 mg/kg ketamine was effective in preventing shivering from developing after general anaesthesia.<sup>11</sup>

Midazolam is a short-acting benzodiazepine that is normally used as an anxiolytic, sedative and anaesthetic adjuvant. Various dosage schemes of intravenous midazolam premedication have previously been published. According to the Canadian Compendium of Pharmaceuticals and Specialties, the recommended dose of midazolam for premedication is 1-1.5 mg (~ 0.02 mg/kg). In the elderly, a total dose of midazolam should not exceed 3.5 mg or 0.07 mg/kg.<sup>12</sup> A few studies have shown that midazolam is safe and effective in producing sedation and anxiolysis at a dose of 0.02 mg/kg, with minimal effects on cardiorespiratory function and oxygen saturation (SpO<sub>2</sub>) in patients.<sup>13,14</sup>

Apart from anxiolysis and sedation, midazolam has also been found to be effective in the prevention of postoperative shivering. Kurz et al found that midazolam produced relatively little impairment of thermoregulatory control, compared to clinical doses of volatile anaesthetics, propofol and alfentanil.<sup>15</sup>

As an alternative to pethidine, a combination of ketamine plus midazolam can be used to prevent shivering. A study demonstrated that a combination of midazolam 0.0375 mg/kg and ketamine 0.25 mg/kg was more effective than ketamine 0.5 mg/kg alone, or midazolam 0.075 mg/kg alone, in preventing shivering from developing during regional anaesthesia.<sup>16</sup> Another study that used a combination of midazolam 0.04 mg/kg and ketamine 0.25 mg/kg, showed a significant reduction in the incidence of shivering, but more sedation, compared to the nefopam and placebo groups.<sup>17</sup>

The purpose of this study was to determine the effectiveness of intravenous midazolam 0.02 mg/kg plus ketamine 0.25 mg/kg, versus midazolam 0.04 mg/kg plus ketamine 0.25 mg/kg, in preventing shivering during spinal anaesthesia for emergency lower limb surgery.

## Method

This prospective, randomised, double-blinded study was conducted after approval from the Dissertation Committee,

Department of Anaesthesiology and Intensive Care, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre (UKMMC), Research and Ethics Committee UKMMC (Project Code No FF-234-2011) and the Medical Research and Ethic Committee of the Ministry of Health, Malaysia (NMRR-10-1225-7599). A total of 90 patients, scheduled for emergency lower limb surgery (patients with fractured femurs, knees, tibias, fibulas or ankles) were recruited and allocated into three groups using computer-generated randomisation: low-dose midazolam plus ketamine (Group A), high-dose midazolam plus ketamine (Group B) and the control (Group C). All patients were American Society of Anesthesiologists (ASA) I and II, aged between 18 and 60 years old. Patients with extensive fractures, massive wounds, burns, or those who had received blood transfusion, were excluded from the study. Patients who were contraindicated for spinal anaesthesia, those with a history of hypo- or hyperthyroidism, significant cardiovascular disease, psychiatric disorders, a history of alcohol or substance abuse, those receiving vasodilators or medication that influences thermoregulation, a history of multiple-drug allergies, patients with an initial body temperature of more than 38.0°C or less than 36.0°C, pregnant patients, or obese patients with a body mass index of more than 35 kg/m<sup>2</sup> were also excluded. Explanations were given and informed consent was obtained from all recruited patients in the study during preanaesthetic assessment.

A venous cannula was inserted into the hand of patients on their admission to the hospital by the respective ward doctor. Patients fasted for at least six hours before surgery. No premedication was administered. The results of routine investigations, including a full blood count, blood urea and serum electrolytes, an electrocardiogram (ECG) and a chest X-ray, were reviewed.

On arrival at the operating theatre, patients underwent standard monitoring, such as noninvasive blood pressure monitoring, a three-leads ECG and a pulse oxymeter. Baseline mean arterial pressure (MAP), heart rate (HR) and SpO<sub>2</sub> were recorded before induction of anaesthesia. Baseline core body temperature was measured using an Omron® infrared ear thermometer (Medizintechnik, Germany).

Spinal anaesthesia was performed with the patients in the sitting position at the L3/L4 or L4/L5 interspaces, with a midline approach using a 27 G spinal needle under aseptic technique. The local anaesthetic agent that was used for spinal anaesthesia comprised 0.5% hyperbaric bupivacaine 12.5-15 mg, with no included opioid. After administration of the spinal anaesthesia, patients were given study drugs depending on the group into which they had been assigned. Patients in Group A were given a combination of intravenous midazolam 0.02 mg/kg and ketamine 0.25 mg/kg, patients

in Group B were administered a combination of midazolam 0.04 mg/kg and ketamine 0.25 mg/kg, and patients in Group C (control) normal saline. All the drugs were prepared and diluted with 5 ml normal saline by the investigators. The attending anaesthesiologists were blinded to the type of drugs used in the study and had been fully briefed on how to grade the severity of shivering during surgery.

All patients were placed in the supine position and actively warmed by using a Bair Hugger™ forced air warming device (Augustine Medical, USA), set at 38°C, with an additional blanket between the patient's skin and the warming device. The upper body was covered by one layer of surgical drapes during surgery. All intravenous fluids were preheated to 37°C and were infused without an intravenous line-warming device. The operating room temperature was maintained at 18-21°C.

The MAP, HR, SpO<sub>2</sub> and core body temperature was recorded during surgery 5, 10, 20 and 30 minutes after administration of the spinal anaesthesia. The same recording of vital signs, except core body temperature, was also carried out in the recovery room. The incidence and severity of shivering during surgery were recorded at the same intervals as core body temperature measurements. Shivering was graded using a scale where 0 = no shivering; 1 = piloerection or peripheral vasoconstriction, but no visible shivering; 2 = muscular activity in one muscle group only; 3 = muscular activity in more than one muscle group, but not generalised; and 4 = shivering affecting the whole body.<sup>2</sup>

Any patient who desaturated to < 95% would be given supplemental oxygen via face mask at 5 l/minute. If a patient continued to shiver with at least grade 3 after spinal anaesthesia and concomitant administration of a selected dose of one of the study drugs, the prophylaxis was considered to be ineffective and intravenous pethidine 25 mg bolus was given as a rescue drug. Any side-effects, such as an alteration in MAP and HR, nausea, vomiting, sweating, nystagmus and hallucination, were recorded. Hallucination was defined as a false sensory experience whereby the patients reported that they saw, heard, smelt, tasted and felt something that was nonexistent. Intravenous metoclopramide 10 mg was administered to patients who developed nausea and vomiting. The degree of sedation was also assessed using a 5-point scale in which 1 = fully awake and orientated; 2 = drowsy; 3 = eyes closed, but arousable to command; 4 = eyes closed, but arousable to mild physical stimulation; and 5 = eyes closed, but unarousable to mild physical stimulation.<sup>16</sup>

Sample size estimation for this study was based on the Power and Sample Size Calculation Programme. Prior data indicated that median incidence of shivering relating to neuraxial anaesthesia in the control group was approximately 55% (an interquartile range of 40-64%). The probability of shivering among treated patients was 15%,

based on a study by Kamal and Hussein.<sup>17</sup> The power of the study was 0.8 and type I error probability equal to 0.05. With an additional dropout rate of 20%, a total of 90 patients were needed, with 30 patients in each group. Demographic data, such as age, gender, race, weight and ASA classification, were detailed. The incidence of shivering within the first 30 minutes and the incidence of adverse reactions of the studied drugs were analysed using the chi-square test. The sedation score was analysed using a nonparametric median test. The alterations in MAP, HR and temperature were analysed using paired Student's t-test for changes within the group and analysis of variance (ANOVA) for repeated measurement in between the groups.

## Results

A total of 90 patients were included in the study. There were 30 patients in each group. Demographic data are shown in Table I. No significant differences were noted with regard to gender, race, age, the weight of the patients and the ASA classification among the three groups.

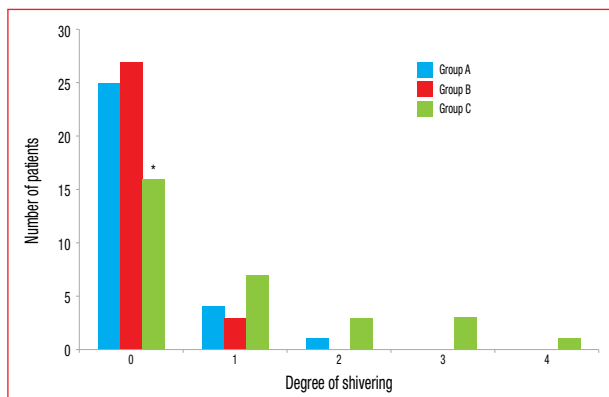
**Table I:** Demographic data

Descriptor	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)
Age (years)	44.2 ± 13.5	38.1 ± 14.9	39.3 ± 15.1
<b>Gender</b>			
Male	23 (76.7)	22 (73.3)	23 (76.7)
Female	7 (23.3)	8 (26.7)	7 (23.3)
<b>Race</b>			
Malay	17 (56.7)	16 (53.3)	20 (66.7)
Chinese	5 (16.7)	2 (6.7)	2 (6.7)
Indian	6 (20)	8 (26.7)	7 (23.3)
Others	2 (6.7)	4 (13.3)	1 (3.3)
<b>ASA classification</b>			
I	13 (43.3)	20 (66.7)	21 (70)
II	17 (56.7)	10 (33.3)	9 (30)
Weight (kg)	68.1 ± 8.2	64.0 ± 9.2	64.7 ± 10.6

Values are expressed as mean ± standard deviation, number (n), and percentage in parenthesis

ASA: American Society of Anesthesiologists

The number of patients who suffered shivering after 30 minutes of spinal anaesthesia according to the different groups of patients and grades of shivering is depicted in Figure 1. A total of 14 patients (46.6%) in Group C showed shivering of various grades. This was significantly higher than that in Groups A and B. There were no significant differences between Groups A and B in terms of absence of shivering, or severity of shivering. Four patients in Group C developed shivering of grade 3 and above. They were given pethidine as rescue therapy, according to protocol. Subsequent observation showed that this treatment abolished the shivering.



\*: p-value = < 0.05

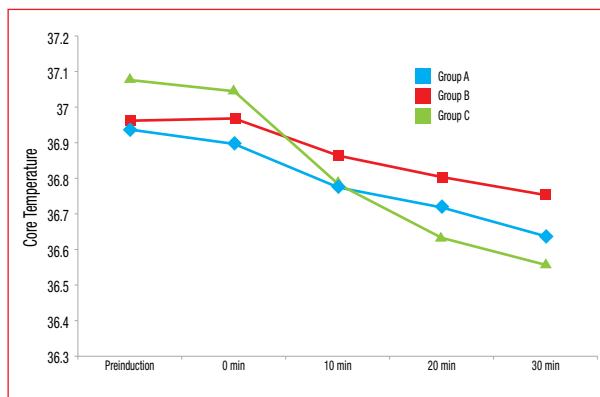
**Figure 1:** The number of patients in each group who suffered from degree of shivering after 30 minutes of spinal anaesthesia

Severity of shivering in relation to time in each group is shown in Table II. No significant difference in severity of shivering was noted between the three groups in the first 10 minutes. However, the number of patients and the severity of shivering were significantly less in Group A and Group B 20 minutes and 30 minutes after spinal anaesthesia, compared to that in Group C (p-value < 0.05). There was no difference between Group A and Group B (p-value > 0.05).

**Table II:** Number of patients with different grades of shivering in the three treatment groups

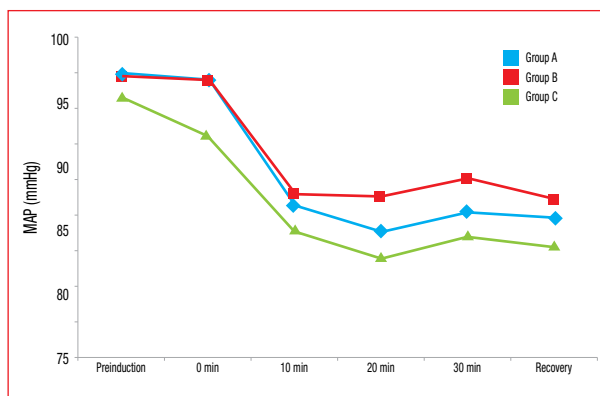
Time	Grade of shivering	Drug			$\chi^2$	P
		Group A	Group B	Group C		
T <sub>0</sub>	Grade 0	30 (100)	29 (96.7)	29 (96.7)	4.02	0.40
	Grade 1	0	0	1 (3.3)		
	Grade 2	0	1 (3.3)	0		
	Grade 3	0	0	0		
	Grade 4	0	0	0		
T <sub>10</sub>	Grade 0	25 (83.3)	28 (93.3)	19 (63.3)	10.17	0.12
	Grade 1	4 (13.3)	2 (6.7)	7 (23.3)		
	Grade 2	1 (3.3)	0	4 (13.3)		
	Grade 3	0	0	0		
	Grade 4	0	0	0		
T <sub>20</sub>	Grade 0	25 (83.3)	27 (90)	17 (56.7)	13.29	< 0.05
	Grade 1	4 (13.3)	3 (10)	7 (23.3)		
	Grade 2	1 (3.3)	0	6 (20)		
	Grade 3	0	0	0		
	Grade 4	0	0	0		
T <sub>30</sub>	Grade 0	25 (83.3)	27 (90)	16 (53.3)	16.39	< 0.05
	Grade 1	4 (13.3)	3 (10)	7 (23.3)		
	Grade 2	1 (3.3)	0	3 (10)		
	Grade 3	0	0	3 (10)		
	Grade 4	0	0	3 (10)		

T<sub>0</sub>: arrival in the operating theatre, T<sub>10</sub>: 10 minutes after spinal anaesthesia; T<sub>20</sub>: 20 minutes after spinal anaesthesia, T<sub>30</sub>: 30 minutes after spinal anaesthesia



**Figure 2:** Changes of mean temperature during the first 30 minutes of surgery

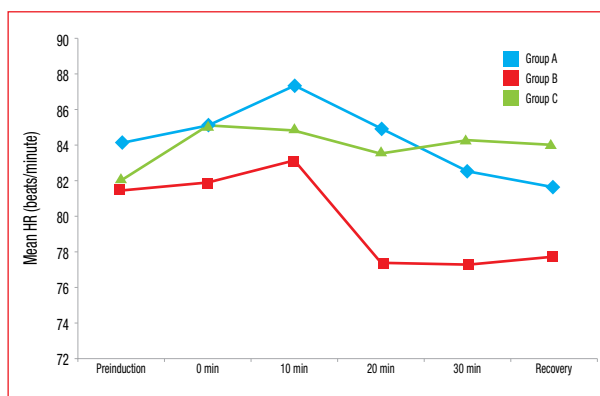
Figure 2 shows significant changes in core body temperature in all three groups within the first 30 minutes of surgery, compared to its baseline temperature values (p-value ≤ 0.001). However, there was no significant difference when comparison was made between groups.



MAP: mean arterial pressure

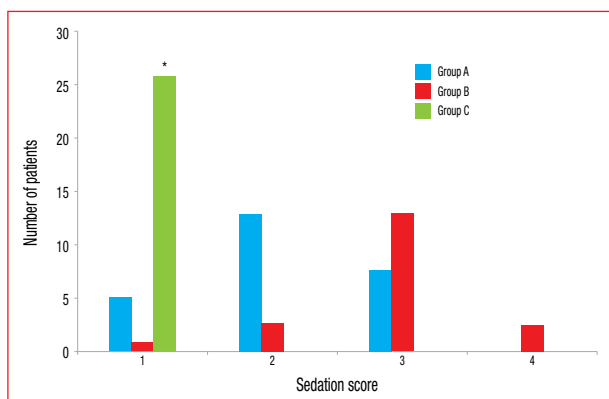
Changes in MAP, HR, SpO<sub>2</sub> and temperature through the surgery were compared within and between the groups. Figures 3 and 4 show changes in MAP and mean HR during surgery, respectively. Using repeated measures, it was established that ANOVA, MAP and mean HR values were not significantly different among the groups at any time during the surgery. None of the patient desaturated during the study period.

**Figure 3:** Changes of mean arterial pressure during surgery in the three groups of patients



HR: heart rate

**Figure 4:** Changes of mean heart rate during surgery in the three groups of patients



\*: p-value < 0.05 compared with the other groups

**Figure 5:** The degree of sedation in all three groups

Figure 5 shows the degree of sedation in all three groups. The sedation score was significantly lower in Group C. All of the patients in this group had a sedation score of 1. Nine patients in Group A (30%) and 15 patients in Group B (50%) had a sedation score of 3. One patient in Group B (3.3%) had a sedation score of 4. The median sedation score in Group A was 2, while it was 3 in Group B. However, there was no significant difference in the sedation score between these two groups. None of the patients had a grade 5 sedation score.

The occurrence of nystagmus was significantly higher in Group A and Group B (p-value < 0.05), compared to that in Group C. One patient in Group A and another in Group B experienced hallucinations, but the result was not statistically significant. None of the results was statistically significant with regard to sweating, nausea and vomiting (Table III).

**Table III:** Side-effects observed between the groups

Side-effects	Group			p-value
	A (n = 30)	B (n = 30)	C (n = 30)	
Nausea and vomiting	1	2	2	0.81
Hallucination	1	1	0	0.60
Sweating	1	0	0	0.36
Nystagmus	14	12	0	< 0.001

Data expressed in number (n)

## Discussion

Shivering that is associated with spinal and epidural anaesthesia is a common and uncomfortable side-effect. It can have potentially detrimental effects, especially in patients with a history of cardiorespiratory disease. These complications include increased oxygen consumption, hypoxaemia, increased carbon dioxide production and lactic acidosis.

Regional anaesthesia produces vasodilatation that facilitates core to peripheral redistribution of heat and loss

of thermoregulatory vasoconstriction below the level of blockade, resulting in an increase in heat loss from the body surfaces.<sup>2</sup> Many studies have been conducted to show the effectiveness of certain drugs in controlling shivering during neuraxial anaesthesia. These drugs include pethidine, ketamine plus midazolam, neostigmine and ketanserin.<sup>17</sup>

The incidence of shivering associated with neuraxial anaesthesia in the control group was 55%, based on a meta-analysis carried out by Crowley and Buggy.<sup>2</sup>

Butwick et al studied the efficacy of intraoperative lower body forced air warming to prevent hypothermia in patients undergoing elective Caesarean delivery under spinal anaesthesia. They found that the incidence of shivering in the forced air warming group was 4 in 15 cases (27%), compared to an incidence of shivering in the control group of 7 in 15 cases (47%). Of the four patients who shivered in the forced air warming group, one patient scored a grade 1, while the other three (20%) recorded a shivering score of 2 or more.<sup>18</sup> It was concluded that intraoperative forced air warming did not prevent perioperative hypothermia, when compared to the control group who did not have forced air warming. They also found that the incidence and intensity of shivering episodes were not significantly different between the two groups.<sup>18</sup>

The findings by Butwick et al are in contrast with those in two other studies that found that the application of a forced air warming device helped to prevent hypothermia.<sup>18</sup> Wagner et al compared two convective warming systems during major abdominal and orthopaedic surgery. Their study proved that convective warming systems did not prevent redistribution hypothermia, but were effective in maintaining perioperative normothermia in patients undergoing major abdominal and orthopaedic surgery with general anaesthesia.<sup>19</sup> Horn et al studied active warming during Caesarean delivery, and reported that patients who received forced air warming had higher core temperatures and fewer shivering episodes than the group receiving passive insulation.<sup>20</sup> However, there were significant differences in the studies, e.g. epidural versus spinal anaesthesia, upper body versus lower body forced air warming, pre-warming (15 minutes of forced air warming before initiation of epidural anaesthesia) versus no pre-warming period, and warmed versus unwarmed intravenous fluids.

Honarmand and Safavi compared placebo, midazolam, ketamine, and a combination of ketamine plus midazolam, in preventing shivering caused by regional anaesthesia, and found that the incidence was 60%.<sup>16</sup> In our study, the incidence of shivering associated with spinal anaesthesia was found to be 46% in the control group, which was higher when compared to patients receiving midazolam plus ketamine. Those in the control group who shivered (14/30 patients), seven patients (23%) had a shivering score of at



least 2. The lower incidence of shivering in our study was probably because all of our patients received active warming with forced air-warming devices in the intraoperative period.

In our study, the mean core body temperature of all three groups was significantly decreased for the first 30 minutes of observation. This significant decrease in temperature, despite active warming, was similar to the findings of Wagner et al.<sup>19</sup> We limited the observation period to the first 30 minutes after spinal anaesthesia to exclude other confounding factors which might have led to shivering, such as a cold ambient operation theatre temperature.<sup>21</sup> The decrease in core temperature in patients receiving placebo was greater than that in the midazolam plus ketamine group.

This is probably an effect of ketamine, a competitive N-methyl-D-aspartic acid (NMDA) receptor antagonist, which is involved in the modulation of thermoregulation at multiple levels. Ketamine, a competitive receptor antagonist of NMDA, plays a role in thermoregulation by different means. Ketamine controls shivering by nonshivering thermogenesis, either by action on the hypothalamus, or by the  $\beta$ -adrenergic effect of norepinephrine. The NMDA receptor acts by modulating the noradrenergic and serotonergic neurons in the locus ceruleus. Also, NMDA receptors modulate ascending nociceptive transmission at the dorsal horn of the spinal cord.<sup>11</sup>

Benzodiazepines have been found to reduce repetitive firing in response to depolarising pulses in the spinal cord neurons of mice. This function may be responsible for suppressing shivering. Among the benzodiazepines, diazepam has been found to be most effective in the prevention of post-spinal shivering.<sup>17</sup> It produces minimal impairment of thermoregulatory control.<sup>15</sup> On the other hand, midazolam reduces core body temperature by inhibiting tonic thermoregulatory vasoconstriction. The core temperature remains relatively unchanged when the two drugs are combined, suggesting that the thermoregulatory effects of the benzodiazepine receptor agonist and the competitive NMDA receptor antagonist oppose each other.<sup>16</sup>

Honarmand and Safavi showed that the prophylactic use of intravenous ketamine 0.25 mg/kg and intravenous midazolam 37.5  $\mu$ g/kg, was more effective than intravenous ketamine 0.5 mg/kg or intravenous midazolam 75  $\mu$ g/kg, in preventing shivering-related regional anaesthesia.<sup>16</sup> Another study by Kamal and Hussein compared the efficacy of nefopam with that of ketamine plus midazolam, and placebo, in the prevention of post-spinal shivering. In their study, patients who were treated with ketamine plus midazolam had an incidence of shivering of 16%. Ten of the 75 patients (13%) showed signs of piloerection and two patients (3%) obtained a shivering score of 2. None of the patients in the ketamine plus midazolam group recorded a shivering score of more than grade 2.<sup>17</sup>

Midazolam has been shown to be effective when used in preoperative sedation.<sup>22</sup> In our study, patients in both the midazolam plus ketamine groups were significantly more sedated than those in the control group. Nine of the 30 patients (30%) in Group A, and 16 of the 30 patients (53%) in Group B, scored more than median.

However, there was no significant difference between the sedation scores in Groups A and B. Sun et al studied the effect of age and gender on midazolam premedication. They compared the effect of two different doses of midazolam 0.02 mg/kg and 0.06 mg/kg on anxiety, sedation and cardiorespiratory outcomes. It was reported that midazolam was effective in producing sedation and anxiolysis at a dose of 0.02 mg/kg, with minimal effect on cardiorespiratory systems and SpO<sub>2</sub> in patients. The patients aged 60-79 years old who received midazolam 0.06 mg/kg showed a significant reduction in mean blood pressure, respiratory rate and SpO<sub>2</sub>.<sup>13</sup> Our study only included patients aged between 18 and 60. In our study, this factor probably contributed to the absence of deleterious effects regarding midazolam sedation, such as respiratory depression, hypoxaemia and apnoea.

The side-effects of ketamine were also noted in this study. Fourteen and 12 patients in Groups A and B, respectively, had nystagmus. One patient in both of these groups experienced psychosis symptoms, such as hallucination. The combination of midazolam and ketamine probably reduced the possibility of patients suffering from hallucination postoperatively. This is consistent with other studies which used a combination of midazolam plus ketamine. Two of 30 patients experienced hallucination in a study by Honarmand and Safavi, while none did in a study by Kamal and Hussein.<sup>16,17</sup> Nausea and vomiting are known side-effects of ketamine and occurred in one and two patients in Groups A and B, respectively. Five patients in Group A and four in Group B had hypotension, and were treated with ephedrine. (In this study, hypotension was defined as a decrease in MAP of more than 20% from baseline). However, there was no significant difference in the incidence of hypotension between these groups, compared to that in the control group.

We acknowledge that our study had limitations. We limited our study to patients who were listed for emergency lower limb surgery. Some of these patients were trauma cases, who had been resuscitated in the emergency department prior to surgery. There was a possibility that they had received large amounts of fluid administered at room temperature, which might have affected baseline core temperature and thermoregulatory function. This was not taken into consideration.

Also, patients scheduled for emergency surgery are considered to be stressed and to have a higher level of

catecholamine, which may have affected thermoregulatory function. A study that involved patients planned for elective surgery under spinal anaesthesia would have eliminated this bias. There were also practical issues with regard to the use of the combination of midazolam plus ketamine as prophylaxis to prevent shivering during spinal anaesthesia. The combination of midazolam plus ketamine involves polypharmacy and errors may occur with drug dilution. Further studies should aim to compare a combination of midazolam plus ketamine with pethidine, as the latter is often used to treat shivering during spinal anaesthesia because it is effective and the drug preparation is easy. It would also be useful to prove that the combination of midazolam plus ketamine is an alternative as prophylaxis against shivering associated with spinal anaesthesia, especially in patients with allergies to pethidine.

In summary, we compared the effects of two different doses of midazolam in combination with ketamine to prevent shivering during spinal anaesthesia for emergency lower limb surgery. A lower midazolam dose of 0.02 mg/kg in combination with ketamine 0.25 mg/kg, was as effective as a combination of a higher midazolam dose of 0.04 mg/kg with ketamine 0.25 mg/kg, in preventing shivering associated with spinal anaesthesia. It was also shown that a combination of lower dose of midazolam plus ketamine was less sedative than a higher dose of midazolam plus ketamine. Future studies are needed to confirm the benefit of the combination of low-dose midazolam plus ketamine in preventing shivering post spinal anaesthesia in the elderly.

## Conclusion

In conclusion, low-dose midazolam 0.02 mg/kg plus ketamine 0.25 mg/kg, had a similar efficacy compared to that of a higher dose of midazolam 0.04 mg/kg plus ketamine 0.25 mg/kg, in preventing shivering during spinal anaesthesia needed for emergency lower limb surgery. There were no significant changes in the haemodynamic parameters in all groups. However, patients in the midazolam plus ketamine groups were more sedated and had a higher incidence of nystagmus.

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