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## Effect of Low-Dose Ketamine on Redistribution Hypothermia during Spinal Anesthesia Sedated by Propofol

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### Abstract

Mild hypothermia is a common complication during spinal anesthesia and may induce a serious adverse outcome. We investigated the effect of low-dose ketamine infusion on the core temperature during spinal anesthesia sedated by propofol infusion. Twenty patients who were scheduled to undergo spinal anesthesia were assigned to one of two groups: after intrathecal injection of bupivacaine, patients who received infusion of ketamine (0.3 mg/kg/hr) and propofol (initial rate of 10 mg/kg/hr) (KP group), and patients who received infusion of placebo (saline) and propofol (initial rate of 10 mg/kg/hr) (P group). The rate of propofol administration was reduced as much as possible while maintaining sedation with an OAA/S score of 3 or below. The core temperature, forearm temperature, and fingertip temperature were recorded before spinal anesthesia, and just before (baseline) and 15, 30, 45, and 60 minutes after the start of propofol administration. The core temperature, reduction in core temperature from baseline ( $\Delta CT$ ), and forearm-fingertip temperature gradient were compared between the two groups. In the P group, the core temperature linearly decreased over time. The core temperature at 30, 45, and 60 minutes was significantly higher in the KP group than in the P group ( $36.3 \pm 0.2$  and  $35.9 \pm 0.3$ , at 60 minutes, mean  $\pm$  SD,  $p < 0.05$ ). The  $\Delta CT$  at 15, 30, 45, and 60 minutes was significantly smaller in the KP group than in the P group. There were no significant differences in the forearm-fingertip temperature gradient between the two groups over the study period. In conclusion, low-dose ketamine administration may confer thermoprotection during spinal anesthesia sedated by propofol.

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**Key words:** hypothermia, spinal anesthesia, ketamine

### Introduction

Vasoconstriction occurs in a cold environment to maintain the core temperature in a narrow range. Spinal anesthesia which lowers the vasoconstriction threshold and inhibits vasomotor tone in the area

with sympathetic blockade, impairs the thermoregulatory function by interrupting afferent thermal input<sup>1</sup>. Consequently, heat distributes from the core to peripheral tissue after induction of general or neuraxial anesthesia. A recent study indicated that 50% of patients who underwent spinal anesthesia became hypothermic as assessed on

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arrival in the recovery room, whether temperature monitoring was performed or not<sup>2</sup>.

Propofol, whether it is used for induction or maintenance of anesthesia, induces peripheral vasodilation, causing core-to-peripheral redistribution of body heat and accelerating the development of core hypothermia induced by spinal anesthesia<sup>3</sup>. Thermoprotection by a second drug administered during spinal or epidural anesthesia has not been demonstrated. A previous study demonstrated that induction of general anesthesia by ketamine administration causes less redistribution hypothermia than induction by propofol administration; this suggests that the increased plasma noradrenaline level induced by ketamine administration may confer thermoprotection during spinal anesthesia<sup>4</sup>. However, hypnosis by sole infusion of ketamine sometimes induces psychedelic effects<sup>5</sup>. Co-administration of ketamine and propofol may reduce the amount of each drug needed to induce and maintain anesthesia, and may confer thermoprotection during spinal anesthesia. We hypothesized that co-administration of low-dose ketamine and propofol may prevent redistribution hypothermia and maintain the core temperature during spinal anesthesia in comparison with administration of propofol alone.

To test this hypothesis, we compared the core temperature and the forearm-fingertip temperature gradient during spinal anesthesia induced by co-administration of ketamine and propofol with those during spinal anesthesia sedated by propofol alone.

## Materials and Methods

### Subjects

Twenty adults of either gender who were scheduled to undergo spinal anesthesia for inguinal hernia repair or conization of the cervix, were recruited to participate in this randomized, placebo-controlled trial. This study was approved by the local ethics committee of Nippon Medical School Second Hospital. After explanation of the purpose of the study, written informed consent was obtained from each patient. Exclusion criteria were morbid obesity, refusal to participate, and presence of a

febrile tendency, cardiopulmonary disease or endocrine disease. All female subjects were postmenopausal. Examination was performed before surgery to avoid the influence of surgical manipulation and positioning. Patients were randomly assigned to one of two groups: (1) those who would receive continuous infusion of ketamine and propofol (KP group), and (2) those who would receive continuous infusion of placebo (saline) and propofol (P group). Premedication consisted of intramuscular injection of 0.5 mg atropine sulfate, 25 mg hydroxyzine, and 15 mg pentazocine, 30 minutes prior to induction of anesthesia.

### Measurement of temperature and anesthesia procedure

The ambient temperature was measured by a thermocouple (Monatherm TM, Tyco Healthcare TM, Mansfield, MA), that was positioned at the level of the patient, well away from any heat-producing products. The ambient temperature in the operating room was kept at approximately 25°C. During examination, subjects were kept supine and covered by cotton blanket and no active warming device was used. The left antecubital vein was secured for infusion of warm acetate ringer solution at 5~10 ml/kg/hr. Routine monitoring included three-lead electrocardiogram, noninvasive monitoring of blood pressure, and pulse oximetry. Before induction of spinal anesthesia, a thermistor patch (Monatherm TM, Tyco Healthcare, TM, Mansfield, MA) was placed on each of the right forearm and tip of the right ring finger to measure the skin surface temperature, and a thermocouple was placed in the external acoustic meatus to measure the core temperature. Skin temperature was measured by a thermistor built in the perioperative monitoring system (BP508 TM, Nihon Kolin TM, Tokyo, Japan). After measurement of vital signs and temperature, intrathecal injection of 0.5% hyperbaric bupivacaine, 2.5~3.0 ml, at Lumber 2/3 interspace was performed with the patient in the left decubitus position to obtain a cephalad dermatomal level of sensory block at the T6 dermatome. Unlabeled syringes that contained the study drug, ketamine, at a concentration of 1 mg/

mL, or placebo (saline) were prepared by an anesthesiologist who did not participate in the present investigation. The anesthesiologist who performed spinal anesthesia, maintained hypnosis, monitored the temperature, and watched the patient for signs of shivering, was not aware of the content of the syringe. Ten minutes after administration of bupivacaine, the dermatomal level of sensory block to cold was checked. After giving reference sensation to C5/C6 dermatome, sensory blockade was confirmed from T10 to T4 dermatome. Alcohol swab was moved from blocked to unblocked area. Testing for sensory blockade was performed just once to avoid the influence of heat loss by alcohol. We started infusion of ketamine or placebo and then propofol. The core temperature, forearm skin temperature, and fingertip skin temperature were recorded at the following time points: before intrathecal administration of bupivacaine, 10 minutes after administration of bupivacaine (baseline; just before the start of administration of ketamine or placebo, and propofol), and every 15 minutes up to 1 hour after starting propofol administration.

#### **Infusion protocol of ketamine and propofol**

After measurement of the baseline values, infusion of ketamine or placebo was started at a rate of 0.3 mg/kg/hr. The rate of ketamine infusion of 0.3 mg/kg/hr had been calculated using the Target Controlled Infusion (Stanpump TM, Steven Shaffer MD, Department of Anesthesiology, University of California, San Diego) to produce a blood concentration of the drug of 100 ng/mL, because ketamine infusion that results in a blood concentration of 150 ng/mL induces a perceptual feeling or unpleasant feeling in patients. Propofol administration was started at a rate of 10 mg/kg/hr immediately after the start of administration of ketamine or the placebo. The eyelash reflex was assessed every 20 seconds after the start of propofol infusion. When the eyelash reflex disappeared, the rate of administration of propofol was reduced to 3 mg/kg/hr. Further, 5 minutes later, the patient's sedation level was reassessed by the anesthesiologist using the Observer's Assessment, Alertness and Sedation (OAA/S) scale<sup>6</sup>; 5 = responds readily to

name spoken in normal tone; 4 = lethargic response to the patient's name spoken in normal tone; 3 = responds only after name is called loudly; 2 = responds only after mild prodding or shaking; 1 = does not respond. When the sedation level was sufficient with an OAA/S score of 1, 2 or 3, the rate of propofol infusion was reduced to 1.5 mg/kg/hr. Thereafter, the rate of propofol infusion was lowered as much as possible while maintaining an OAA/S score of 1, 2 or 3. An incremental bolus of ephedrine, 6 mg, was administered intravenously when the systolic pressure fell below 90 mmHg.

#### **Statistical analysis**

We obtained pilot data from 8 patients (n=4 in each group). From the pilot data, it was determined that eight patients in each group were sufficient to test the assumption that the difference in the core temperature at 60 min after propofol administration compared with that at baseline in the KP group is half of that in the P group using power analysis ( $\alpha=0.05$ ,  $\beta=0.2$ ). Delta CT was defined as the difference between the core temperature at baseline and the core temperature at 15, 30, 45 or 60 min. The forearm-fingertip temperature gradient was defined as the difference between the skin surface temperature of the forearm and the skin surface temperature of the fingertip. The core temperature at the forearm-fingertip temperature gradient become positive indicated the vasoconstriction threshold. The blood pressure, heart rate, core temperature, delta CT, and forearm-fingertip temperature gradient before spinal anesthesia, at baseline, and at 15, 30, 45 and 60 minutes after the start of propofol administration were compared between the KP and P groups using analysis of variance for repeated measures. Difference between the groups in the core temperature at 60 minutes and average dose of propofol were tested using analysis of covariance. The number of patients who required ephedrine administration to maintain the blood pressure in the KP and P groups was compared using the chi-squared test. The changes in the forearm-fingertip temperature gradient as well as changes in the core temperature were examined in each group using

Table 1 Demographic data of the patients

	Group P (n = 10)	Group KP (n = 10)	p
Age (years), median (range)	54 (21 ~ 72)	55 (20 ~ 71)	NS
Weight (kg) mean ± SD	60 ± 6	56 ± 8	NS
Height (cm) mean ± SD	165 ± 7	160 ± 9	NS
Gender (male : female)	8 : 2	6 : 4	NS
Cephalad level of block	T6 (T5 ~ T6)	T6 (T4 ~ T6)	NS
Ambient temperature (°C)	25.6 ± 0.8	24.9 ± 0.7	NS
Average dose of propofol (mg/kg) mean ± SD	2.7 ± 0.5	2.2 ± 0.7	<0.05
Number of patients who required ephedrine administration	2	3	NS

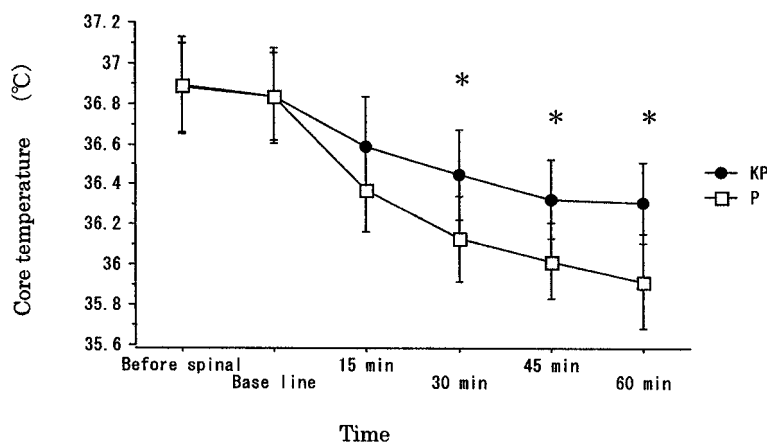


Fig. 1 Changes in core temperature before and after induction of spinal anesthesia with ketamine and propofol (KP group), or propofol alone (P group) up to 60 min after the start of propofol administration. Data are expressed as mean ± 95% CI. \*: p < 0.05 versus P group at the respective time point.

ANOVA. Differences were considered to be significant at a level of p < 0.05.

### Results

All patients were able to complete the study without any complications. There were no demographic differences between the KP and P groups (Table 1). After administration of bupivacaine, the blood pressure gradually decreased over time and there were no significant differences in the blood pressure between the two groups at the respective time points [from 131 ± 20 (mean ± SD) to 101 ± 8 in P group (n = 10); and from 133 ± 18 to 108 ± 13 in KP group (n = 10), from before spinal anesthesia to 60 minutes]. The heart rate was stable during the anesthesia in both groups (67 ± 11 and 70

± 15 in P group; and 69 ± 16 and 73 ± 13 in KP group, before spinal anesthesia and at 60 minutes). The number of patients who required ephedrine administration did not significantly differ between the two groups (Table 1). The core temperature decreased by 0.9 ± 0.1°C in the P group and by 0.5 ± 0.1°C in the KP group at 60 min after the start of propofol administration in comparison with baseline values. The core temperature of the P group was significantly lower than that of the KP group at 30, 45 and 60 minutes after the start of propofol administration (p < 0.05 at each time point, Fig. 1). The average dose of propofol administered over the 60-min study period in the KP group was significantly less than that in the P group (2.2 ± 0.7 mg/kg vs. 2.7 ± 0.5 mg/kg, p < 0.05; Table 1). However, the average dose of propofol administered

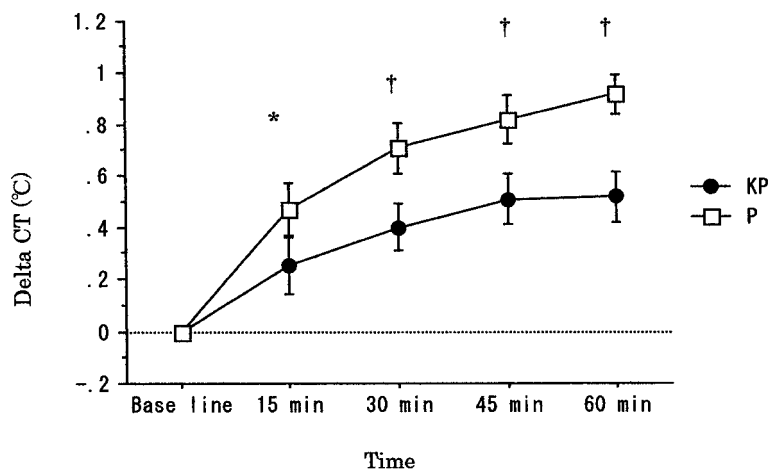


Fig. 2 Changes in delta CT before and after induction of spinal anesthesia with ketamine and propofol (KP group), or propofol alone (P group) up to 60 min after the start of propofol administration. Data are expressed as mean  $\pm$  95% CI.

\*:  $p < 0.05$  versus P group at the respective time point.

†:  $p < 0.001$  versus P group at the respective time point.

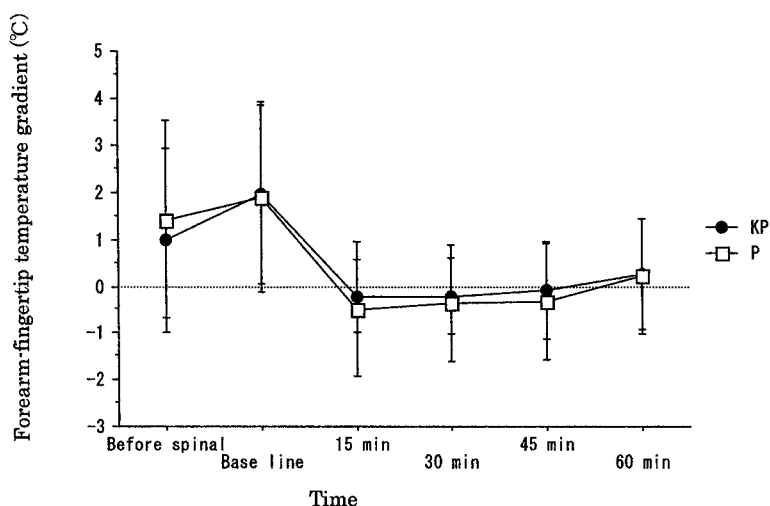


Fig. 3 Changes in the forearm-finger tip temperature gradient before and after induction of spinal anesthesia with ketamine and propofol (KP group), or propofol alone (P group). Data are expressed as mean  $\pm$  95% CI. No significant differences between the KP and P group were found.

was not a covariate for the difference in core temperature at 60 minutes. The delta CT was significantly smaller in the KP group than in the P group at 15, 30, 45, and 60 minutes ( $p < 0.05$ ,  $p < 0.001$ ,  $p < 0.001$ ,  $p < 0.001$ ) (Fig. 2).

There was wide variation in the forearm-fingertip temperature gradient among the patients in each group (Fig. 3). Before spinal anesthesia and at

baseline, the forearm-fingertip temperature gradient was positive in nearly all patients, indicating vasoconstriction. However, at 15 minutes after initiation of propofol administration, many patients in both groups seemed to be vasodilated. At 60 minutes after initiation of propofol administration, some patients in both groups seemed to be vasoconstricted. However, there was wide variation

in the forearm-fingertip temperature gradient among the patients in the KP and P groups and there were no significant differences in the forearm-fingertip temperature gradient between the KP and P groups at any time point in the study.

### Discussion

Sympathetic blockade by epidural or spinal anesthesia induces an increase in apparent leg temperature and inhibits thermoprotection. Peripheral vasodilation in the lower extremities during spinal or epidural anesthesia causes compensatory vasoconstriction in the upper extremities to maintain the core temperature. The administration of hypnotics or opioids attenuates this thermoregulatory action<sup>7</sup>. The reduction in the vasoconstriction threshold upon spinal or epidural anesthesia is reported to be approximately 0.5°C<sup>8</sup>. Propofol influences thermoregulatory control by reducing the vasoconstriction and shivering thresholds, as well as by causing sympathoinhibition-induced vasodilation<sup>9,10</sup>. Studies *in vitro* suggest that propofol induces vasodilation by relaxing vascular smooth muscle<sup>11</sup>. The blood concentration of propofol in the patients in the P and KP groups was estimated to be between 1 mg/ml and 2 mg/ml. It is suspected that in both groups, the vasoconstriction threshold may have been reduced by over 1°C through the interaction of spinal anesthesia and propofol infusion. Propofol, with or without ketamine, caused vasodilation by reducing the constriction threshold to below the core temperature.

The core temperature was maintained to a greater extent in the KP group than in the P group. The average dose of propofol infused during the observation period was significantly smaller in the KP group than in the P group; however, the degree of the reduction in the average propofol dose was only 20%. The lack of influence of the average dose of propofol administered on core temperature at 60 minutes as shown in analysis of covariance suggests that maintenance of the core temperature in the KP group may not be related to the reduction in the amount of propofol administered. The changes in the forearm-fingertip temperature gradient in our study

were similar to those obtained in the study demonstrating the effect of phenylephrine infusion during general anesthesia<sup>12</sup>. The forearm-fingertip temperature gradient in both groups was a negative value until 45 minutes. However at 60 minutes, although the magnitude was small, the tip temperature value of the forearm-fingertip gradient became positive, indicating that in some patients, vasoconstriction occurred in the upper extremities. The dose of propofol in both groups was reduced as much as possible, and in some patients the core temperature fell below the vasoconstriction threshold. The lack of significant differences in the forearm-fingertip temperature gradient between the groups indicates that the core temperature was not maintained by vasoconstriction in the upper extremities in the KP group. However, the core temperature at 60 minutes, when in some patients vasoconstriction occurs in the upper extremities, was higher in the KP group. This indicates the probability that in the KP group, the vasoconstriction threshold was maintained at a higher temperature than that in the P group.

During ketamine administration, the plasma norepinephrine level increases, while the tone of the sympathetic nerve decreases. *In vitro* and *in vivo* studies on ketamine suggest that the degree of the increase in plasma norepinephrine level is dose-dependent<sup>13</sup>. Although ketamine has been reported to inhibit noradrenaline reuptake and stimulate non-exocytotic noradrenaline release from nerve endings<sup>14,15</sup>, the mechanism of the dissociation between the noradrenaline level and sympathetic activity is not known. Studies demonstrating stabilized hemodynamic consequence by co-administration of ketamine and propofol during spinal anesthesia suggest that ketamine administration may increase the plasma level of noradrenaline<sup>16,17</sup>.

The dose of ketamine in the present study may have been too low to increase the blood pressure; however, a mild vasopressor effect may change the distribution of blood flow.

The dose of ketamine infusion in our study was approximately 10% of the dose for maintenance of ketamine anesthesia. The higher dose of ketamine,

even if it induces vasoconstriction, may induce increase in cardiac output simultaneously. This increase in cardiac output may increase the heat flow to peripheral tissues from the central component and may induce conflicting results. Again, there were no significant differences in the forearm-fingertip temperature gradient in the upper body between the KP and P groups throughout the study period. Even if vasoconstriction had been induced in the upper body, the contribution of vasoconstriction limited to the upper body may not be large, because the area of the upper body that was not blocked by spinal anesthesia may have been very small compared to the area of the lower body. Ketamine may induce thermoprotection by changing the vasomotor tone or blood flow distribution in the area sympathetically blocked by spinal anesthesia.

In conclusion, co-administration of low-dose ketamine may confer thermoprotection during spinal anesthesia sedated by propofol.

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