

Influence of Midazolam and Glycopyrrolate on Intra-operative Body Temperature in Abdominal Surgical Patients

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Purpose: Influence of benzodiazepine (midazolam) or cholinergic inhibitor (atropine or glycopyrrolate) on intra-operative body temperature remains unclear and controversial. This study compares intra-operative body temperature in 50 abdominal surgical patients under general anesthesia between the administration of midazolam and glycopyrrolate in combination, or glycopyrrolate alone. **Methods:** Patients who underwent abdominal surgery were recruited from September 2008 through October 2009 at Gachon University Gil hospital in Incheon. Core body temperature was measured in the right ear using a tympanic membrane thermometer at induction of general anesthesia and at 1 hr, 2 hr, and 3 hr after induction. **Results:** There were no differences in core body temperature at any measurement point between either patient group ($F = 1.08, p = .377$). Core body temperature decreased throughout the 3 hr after induction in both groups ($F = 9.22, p < .001$). Specially, core temperatures at induction of general anesthesia ($p < .001$), 1 hr ($p < .001$), 2 hr ($p < .001$), and 3 hr ($p < .001$) after induction were lower than before administration of midazolam and glycopyrrolate, or glycopyrrolate alone. **Conclusion:** We conclude that a cholinergic inhibitor (glycopyrrolate, 0.1 mg) therefore seems not to affect intra-operative body temperature of patients given a benzodiazepine (midazolam, 0.04 mg kg⁻¹), and not to increase body temperature in patients not given a benzodiazepine during the 3 hr after the induction of general anesthesia. Intra-operative warming therefore is needed to prevent hypothermia in surgical patients who receive pre-operative administration of midazolam and/or glycopyrrolate.

Key Words: Glycopyrrolate; Hypothermia; Intra-operative care; Midazolam

INTRODUCTION

Hypothermia is defined as having a core body temperature less than 36°C (Insler, O'Connor, Leventhal, Nelson, & Starr, 2000; Karalapillai & Story, 2008; Sessler, 2001). Intra-operative hypothermia is a common perioperative complication of surgery in which body cavities are exposed to ambient temperature. The risk factors of intra-operative hypothermia include major surgery such as abdominal, thoracic, spine and hip arthroplastic operation, blood transfusion, duration of surgery >2-3 hr, combined epidural and general anesthesia, age >70 yr, low pre-oper-

ative body temperature, and an ambient temperature in the operating room <21.3°C (Flores-Maldonado et al., 1997; Frank et al., 1992; Poveda, Galvão, & dos Santos, 2009). Intra-operative hypothermia increases the risk of surgical wound infection (Flores-Maldonado et al., 1997; Frank et al., 1992; Poveda, Galvão, & dos Santos, 2009), decreases immune responses (Matsui, Ishikawa, Takeuchi, Okabayashi, & Maekawa, 2006; Qadan et al., 2009), impairs coagulation (Rohrer & Natale, 1992), and stimulates cardiac arrhythmia (Frank et al., 1997). A nurse anesthetist takes an important role in preventing intra-operative hypothermia.

Midazolam is a benzodiazepine class compound that is commonly administered for sedation. The association of midazolam and hypothermia has been studied since Irvine (1966) reported the death of an 84-year-old male patient due to accidental hypothermia after administration of diazepam (another benzodiazepine). However, the data about accidental hypothermia have been equivocal. Taylor, Little, Nutt, and Sellars (1985)

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reported the hypothermic effect of a benzodiazepine on rodents, and Matsukawa et al. (1997) concluded that midazolam impeded thermoregulatory vasoconstriction and produced core-to-peripheral heat redistribution and hypothermia. In addition, Matsukawa et al. (2001) reported that cholinergic inhibitors (atropine or glycopyrrolate) were associated with an increase in core temperature of 0.3°C, while a combination of midazolam and atropine did not affect core temperature 30 min after administration. The authors concluded that cholinergic inhibitors opposed the thermoregulatory effects of the benzodiazepine receptor agonist, preventing midazolam-induced core hypothermia in elderly patients. The net effect is to leave core temperature unchanged.

On the other hand, Kurz et al. (1995) demonstrated that midazolam produced little impairment of thermoregulatory control. Moreover, Toyota, Sakura, Saito, Ozasa, and Uchida (2004) asserted that midazolam as premedication could reduce intra-operative heat loss. Furthermore, Park and Yoon (2007) reported that the combination of midazolam and glycopyrrolate decreased intra-operative core temperature by 0.3°C, even though the patients received warm fluid intravenously. In light of the studies by Kurz et al. (1995), Toyota et al. (2004) and Park and Yoon (2007), a benzodiazepine (midazolam) seems to attenuate, rather than produce, intra-operative hypothermia, and a cholinergic inhibitor (glycopyrrolate) seems not to prevent intra-operative hypothermia.

The relationship between intra-operative body temperature and a benzodiazepine or a cholinergic inhibitor still remains unclear and controversial. To prevent hypothermia during anesthesia, monitoring body temperature is an important role of the nurse anesthetist. The present study therefore compared intra-operative body temperature for 3 hr after induction of general anesthesia in a small group of Korean patients undergoing abdominal surgery. Patients were administered either midazolam and glycopyrrolate, or glycopyrrolate alone.

METHODS

1. Research design

This prospective research was conducted in Incheon, Korea, from September 2008 to October 2009.

2. Setting and samples

All participants were American Society of Anesthesiologists (ASA) physical status I (a normal healthy patient) or II (a patient with mild sys-

temic disease), and were recruited by an advertisement posted from September 2008 through October 2009 at Gachon University Gil hospital. All participants underwent elective abdominal surgery under general anesthesia. On the basis of previous studies, the risk factors for the development of hypothermia or decreased body temperature in the peri-operative period include low body mass index (BMI), low total body fat, low body surface area, ASA physical status III or IV, and a history of diabetic neuropathy (Kitamura, Hoshino, Kon, & Ogawa, 2000; Kongsayrepong et al., 2003; Kurz et al., 1995; Poveda et al., 2009; Yamakage et al., 2000). In addition, thyroid disease affects cardiovascular function or the balance of body heat, and Raynaud's disease leads to peripheral vasoconstriction. We therefore included patients with age >20 yr, BMI >18.5 kg m⁻², consciousness, and ASA class I or II, who were to be administered glycopyrrolate for premedication, and were to undergo anesthesia for more than 3 h. We excluded patients with a history of diabetes mellitus, thyroid disease or Raynaud's disease; who had pre-operative use of clonidine (phenothiazine), meperidine, or intra-operative blood transfusion.

Midazolam is usually administered to relieve pre-operative anxiety; glycopyrrolate to prevent pulmonary aspiration during the induction of general anesthesia. At the time of patient recruitment, not all anesthesiologists at Gachon University Gil Hospital routinely prescribed a benzodiazepine (midazolam) to surgical patients under general anesthesia. Although some anesthesiologists prescribed midazolam as premedication to older surgical patients with an ASA physical status I or II, other anesthesiologists did not. On the other hand, premedication involving a cholinergic inhibitor (glycopyrrolate) was given to all surgical patients under general anesthesia. We therefore measured the body temperature of surgical patients during anesthesia after the administration of midazolam and glycopyrrolate, or glycopyrrolate alone.

The initial 140 patients with an ASA I or II physical status comprised 74 patients prescribed midazolam and glycopyrrolate, and 66 patients prescribed glycopyrrolate alone. By matching patients' age, gender, and ASA class, 27 patients assigned to the midazolam and glycopyrrolate group, and 27 patients to the glycopyrrolate group. For example, if one patient who was female, in her fifties and ASA class I was allocated to the midazolam and glycopyrrolate group, another patient who was female, in her fifties and ASA class I was allocated to the glycopyrrolate group. Similarly, if a male, ASA class II patient, in his sixties was allocated to the midazolam and glycopyrrolate group, another patient who was male, in his

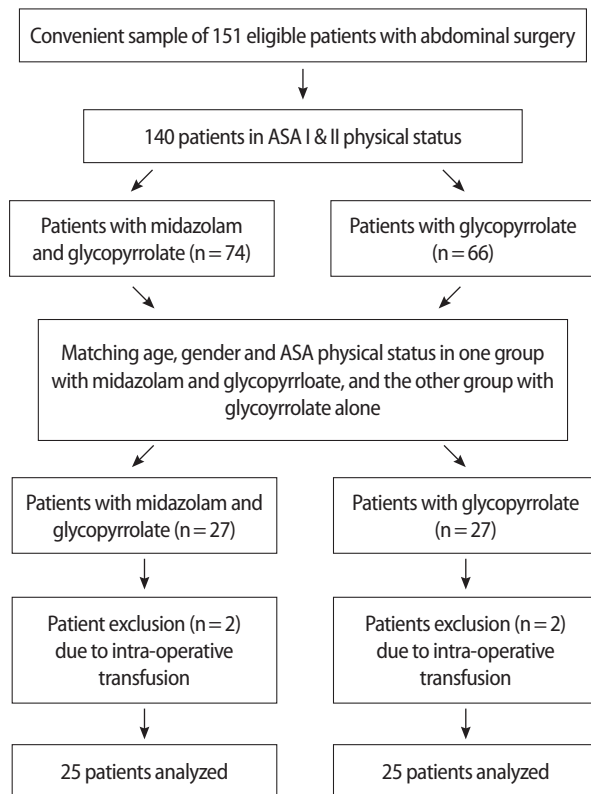


Figure 1. Flow diagram of study participants between combination of midazolam and glycopyrrolate, and glycopyrrolate alone.

sixties and ASA class II was allocated to the glycopyrrolate group. Fifty of fifty-four patients (92.6%) completed the study (Figure. 1). Four patients were withdrawn from the study because they received a blood transfusion during their surgery; two of these patients belonged to the midazolam and glycopyrrolate group, and two to the glycopyrrolate group, respectively. The final number of patients studied was 50; 25 of whom received midazolam and glycopyrrolate, and 25 glycopyrrolate alone.

3. Procedures

1) Recruitment of subjects

The protocol was approved by the Ethics and Research Committee of Gachon University Gil Hospital (IRB No: 200809-03-1008). All abdominal surgical patients were fully informed about the purpose, nature, design and duration of the study during the pre-operative interview, and their written consent was then obtained.

2) Administration of Midazolam or glycopyrrolate

Midazolam (0.04 mg kg⁻¹) or glycopyrrolate (0.2 mg) were adminis-

tered intramuscularly to the patients in the ward 30 min before their transfer to the operating room.

3) Technique of general anesthesia and warming of patients during operation

General anesthesia was performed with a standardized technique. Each patient was administered intravenous propofol (1.5 mg kg⁻¹), rocuronium (1 mg kg⁻¹), and alfentanil (10 µg) for induction of general anesthesia, and then the trachea was intubated. Anesthesia was maintained with isoflurane (1.5-2.0%) in nitrous oxide (2 L min⁻¹), and oxygen (2 L min⁻¹). Ventilation was mechanically controlled at a rate and volume sufficient to maintain end-tidal PCO₂ near 35 mmHg.

The flow of oxygen was maintained at 2 L min⁻¹ via a semi-closed circle system, and an airway heating exchanger (Heated Circuit Kit A 4488; Ace Medical, Seoul, Korea) set to 40°C. Warming of the patients began immediately after the induction of anesthesia using a full-length circulating-water mattress (Blanketrol; Cincinnati Sub-Zero, Cincinnati, OH, USA). A circulating water mattress was set to 38°C, which was placed under the patient's back. Warming was maintained throughout anesthesia, and each patient was covered with a single surgical drape of cotton cloth.

Lactated Ringer's solution was maintained at the ambient temperature of the operating room (23-25°C with relative humidity 30-50%), and was infused at approximately 5-8 mL kg⁻¹ h⁻¹. At the commencement of skin suture, the neuromuscular blockade was reversed with neostigmine (1.0 mg) and atropine (1.0 mg), and the trachea was extubated.

4. Power calculation

Effect size was calculated as 0.492 and 0.599 being based on the respective studies of Matsukawa et al. (2001, 2003). With an effect size of 0.492, an alpha of 0.05 and a power of 0.8, at least 25.4 study participants for each group were required for the present study to have statistically predictive power. With an effect size of 0.599, 17.2 study participants were required. Consequently, we selected a total of 50 surgical patients for this study, 25 subjects with administration of midazolam and glycopyrrolate, and 25 subjects with administration of glycopyrrolate alone.

5. Measurements

Demographic data including gender, age, ASA class, disease, weight, and height were collected. BMI was calculated by the Kauff Index {weight (kg)/ height (m)²}, body surface area (BSA) was calculated by the

Dubois Index $\{0.20247 \times \text{height (m)}^{0.725} \times \text{weight (kg)}^{0.425}\}$, lean body mass (LBM) was calculated by the Hatfield formula [LBM in Female = $\{1.07 \times \text{weight (kg)} - 128 \times (\text{weight (kg)}^2 / \text{height (cm)}^2)\}$; LBM in male = $\{1.10 \times \text{Weight (kg)} - 128 \times (\text{Weight (kg)}^2 / \text{Height (cm)}^2)\}$], and total body fat was calculated from LBM fat [TBF (%) = $(\text{kg-LBM}) / \text{kg} \times 100$].

Thirty minutes before patient's transfer to the operating room, the basal tympanic membrane temperature (TMT) was measured in the right ear using a Thermo Scan IRT-4520 tympanic membrane thermometer (Braun, Frankfurt, Germany). Surgical patients were then intramuscularly administered a combination of midazolam (0.04 mg kg⁻¹) and glycopyrrolate (0.2 mg), or glycopyrrolate (0.2 mg) alone. Upon transportation to the operating room, patient's blood pressure and heart beat were monitored, and an electrocardiogram recorded using a Dash 4000 ECG monitor (GE, New York, NY, USA) throughout general anesthesia. Pre-operative systolic blood pressure, heart beat, and TMT were measured immediately before induction of anesthesia. TMT was again measured 1 hr, 2 hr, and 3 hr following the induction of general anesthesia. The ambient temperature and relative humidity in the operating room were measured 1 hr after the induction of anesthesia. Finally, the duration of anesthesia, the volume of irrigation fluid for the abdominal cavity, and the amount of estimated blood loss were recorded at the end of the operation.

6. Data analyses

SPSS for Windows (Version 16.0; SPSS, Chicago, IL, USA) statistical software was used to analyze the data. The Chi-square test and Student's t-test were used to confirm homogeneity of the demographic and physiological characteristics between the group administered the combination of midazolam and glycopyrrolate, and the group administered glycopyrrolate alone. The repeated measures ANOVA were used to compare intra-operative TMT between the two groups for 3 hr after induction of anesthesia. In addition, we used the Bonferroni multiple comparison among the times of TMT measurement.

RESULTS

1. Demographic and physiologic characteristics

The results of the homogeneity test for the demographic and clinical physiological characteristics of the two groups are presented in Table 1. The Chi-square test for gender, ASA physical status, disease, and the

type of operation showed no statistically significant differences between the two groups (Table 1). In addition, age, pre-operative systolic blood pressure, heart beat, pre-operative TMT, ambient temperature in the operating room, duration of anesthesia, volume of irrigation fluid for the abdominal cavity, and estimated blood loss showed no statistically significant differences between the two groups. Furthermore, BMI, BSA, LBM, and TBF for the two groups were similar. Pre-operative TMT was almost similar in both groups; 36.95°C in the group administered glycopyrrolate alone and 36.82°C in the group administered combination of midazolam and glycopyrrolate ($t = 1.69, p = .096$).

2. Effect of midazolam or glycopyrrolate on TMT

The effect of midazolam or glycopyrrolate on intra-operative TMT is

Table 1. Homogeneity Test for Physiological Characteristics (N = 50)

| Characteristic | Group | | t or X ² | p |
|------------------------------------|-----------------------|-----------------------|---------------------|------|
| | G (n = 25) | M & G (n = 25) | | |
| | Mean ± SD Or N (%) | Mean ± SD Or N (%) | | |
| Age (yr) | 57.8 ± 13.8 | 57.7 ± 10.8 | 0.03 | .973 |
| ≤ 30 | 1 (2.0) | 1 (2.0) | - | - |
| 31-40 | 2 (4.0) | 2 (4.0) | | |
| 41-50 | 2 (4.0) | 2 (4.0) | | |
| 51-60 | 7 (14.0) | 7 (14.0) | | |
| 61-70 | 11 (22.0) | 11 (22.0) | | |
| 71-80 | 2 (4.0) | 2 (4.0) | | |
| Gender | 12 (48.0) | 12 (48.0) | - | - |
| Female | 13 (52.0) | 13 (52.0) | | |
| Male | 12 (48.0) | 13 (52.0) | | |
| ASA physical status | 12 (48.0) | 13 (52.0) | - | - |
| I | 13 (52.0) | 13 (52.0) | | |
| II | 12 (48.0) | 13 (52.0) | | |
| Disease | 12 (48.0) | 11 (44.0) | 0.08 | .777 |
| Stomach ca | 13 (52.0) | 14 (56.0) | | |
| Colon & Rectal ca | 13 (52.0) | 14 (56.0) | | |
| Operation | 13 (52.0) | 9 (36.0) | 1.35 | .509 |
| Mastectomy | 4 (16.0) | 6 (24.0) | | |
| Mile's operation | 8 (23.5) | 10 (21.6) | | |
| Colectomy | 132.2 ± 12.9 | 131.7 ± 14.4 | 0.12 | .902 |
| Preoperative SBP (mmHg) | 77.3 ± 16.8 | 72.0 ± 11.4 | 1.31 | .197 |
| Preoperative heart rate (beat/min) | 36.95 ± 0.28 | 36.82 ± 0.27 | 1.69 | .096 |
| Preoperative BT (°C) | 23.3 ± 1.41 | 23.3 ± 1.34 | -0.51 | .959 |
| Ambient temperature (°C) | 56.4 ± 8.6 | 55.2 ± 6.7 | 0.53 | .597 |
| Relative humidity (%) | 4.57 ± 0.93 | 4.85 ± 1.11 | -0.98 | .332 |
| Anesthetic time (hr) | 2,652 ± 1,574 | 3,012 ± 1,410 | -0.85 | .399 |
| Irrigation fluid (mL) | 340.0 ± 232.3 | 418.8 ± 286.9 | -1.07 | .291 |
| Estimated blood loss (mL) | 22.4 ± 2.7 | 22.0 ± 2.6 | 0.49 | .622 |
| BMI (kg/m ²) | 1.66 ± 0.16 | 1.61 ± 0.14 | 1.11 | .272 |
| BSA | 36.3 ± 2.73 | 35.6 ± 2.40 | 0.96 | .343 |
| Weight/BSA | 48.1 ± 7.52 | 45.9 ± 6.70 | 1.07 | .289 |
| Lean body mass | 20.7 ± 4.86 | 20.4 ± 5.19 | 0.17 | .869 |
| TBF (%) | | | | |

G = glycopyrrolate; M & G = midazolam and glycopyrrolate; ASA = American society of anesthesiology; BMI = body mass index; BSA = body surface area; TBF = total body fat.

summarized in Table 2 and Figure 2. There were no differences in the change pattern of TMT intra-operatively 3 hr following the induction of general anesthesia between the groups ($F = 1.08, p = .377$).

However, following the induction of anesthesia, TMT decreased continuously in both groups throughout the 3 hr post-induction period ($F = 127.6, p < .001$). Specially, TMT at induction ($p < .001$), and at 1 hr ($p < .001$), 2 hr ($p < .001$), and 3 hr ($p < .001$) after induction were lower than before administration of midazolam or glycopyrrolate in either group.

Although TMT in the glycopyrrolate group was slightly higher than in the midazolam and glycopyrrolate group, the differences were not statistically significant ($F = 3.57, p = .065$).

TMT in the group administered glycopyrrolate was significantly greater than in the group administered midazolam and glycopyrrolate after induction of anesthesia ($p < .05$).

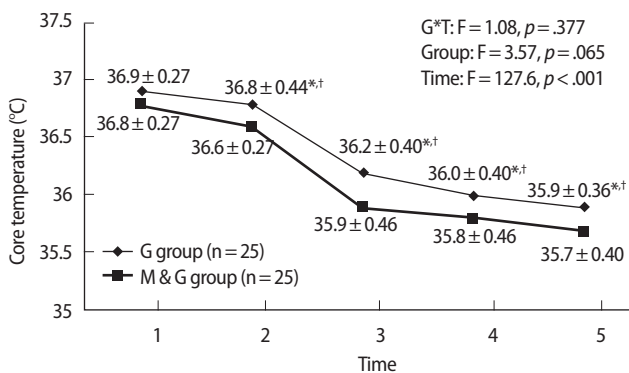


Figure 2. Intra-operative tympanic membrane temperature between combination of midazolam and glycopyrrolate, and glycopyrrolate alone. * $p < .001$; †comparison of core body temperature between time 1 and each time; G group = administration of glycopyrrolate; M & G group = administration of midazolam and glycopyrrolate; G*T = group*time; Time 1 = before administration of midazolam or glycopyrrolate; Time 2 = immediately after induction of anesthesia; Time 3 = 1 hr after induction; Time 4 = 2 hr after induction; Time 5 = 3 hr after induction.

3. Incidence of hypothermia for 3 hr after induction of general anesthesia

Incidence rate of hypothermia for 3 hr after induction of general anesthesia is summarized in Table 3. The incidence rate for hypothermia at 1 hr, 2 hr and 3 hr after induction of general anesthesia was 34 %, 44%, and 60% in the entire group administered glycopyrrolate, or in the group administered combination of midazolam and glycopyrrolate, respectively.

DISCUSSION

Hypothermia is the most common intra-operative complication of general anesthesia. Previous studies reported a relationship between an-

Table 3. Incidence of Hypothermia < 36°C in Tympanic Membrane Temperature

| Period | G group (n = 25) | M & G group (n = 25) | Total (n = 50) | χ^2 | p |
|--------|---------------------|-------------------------|-------------------|----------|------|
| | n (%) | n (%) | n (%) | | |
| Time 1 | | | | | |
| No | 25 (100) | 25 (100) | 50 (100) | - | - |
| Yes | 0 (0) | 0 (0) | 0 (0) | | |
| Time 2 | | | | | |
| No | 25 (100) | 25 (100) | 50 (100) | - | - |
| Yes | 0 (0) | 0 (0) | 0 (0) | | |
| Time 3 | | | | 2.23 | .136 |
| No | 19 (76) | 14 (56) | 33 (66) | | |
| Yes | 6 (24) | 11 (44) | 17 (34) | | |
| Time 4 | | | | 0.33 | .569 |
| No | 15 (60) | 13 (52) | 28 (56) | | |
| Yes | 10 (40) | 12 (48) | 22 (44) | | |
| Time 5 | | | | 5.33 | .021 |
| No | 14 (56) | 6 (24) | 20 (40) | | |
| Yes | 11 (44) | 19 (76) | 30 (60) | | |

G group = administration of glycopyrrolate; M & G group = administration of midazolam and glycopyrrolate; Time 1 = before administration of midazolam or glycopyrrolate; Time 2 = immediately after induction of anesthesia; Time 3 = 1 hr after induction; Time 4 = 2 hr after induction; Time 5 = 3 hr after induction.

Table 2. Intra-operative Tympanic Membrane Temperature between Combination of Midazolam and Glycopyrrolate, and Glycopyrrolate Alone

| Group | Core body temperature (°C) | | | | | Source | F | p |
|----------------------|----------------------------|-----------------------|-----------------------|-----------------------|-----------------------|--------|--------|-------|
| | Time 1 Mean ± SD | Time 2*† Mean ± SD | Time 3*† Mean ± SD | Time 4*† Mean ± SD | Time 5*† Mean ± SD | | | |
| G group (n = 25) | 36.9 ± 0.27 | 36.8 ± 0.44 | 36.2 ± 0.42*† | 36.0 ± 0.40 | 35.9 ± 0.36 | Group | 3.57 | .065 |
| M & G group (n = 25) | 36.8 ± 0.27 | 36.6 ± 0.27 | 35.9 ± 0.42 | 35.8 ± 0.46 | 35.7 ± 0.40 | Time | 127.60 | <.001 |
| | | | | | | G*T | 1.08 | .377 |

* $p < .001$; †comparison of core body temperature between time 1 and each time.

G group = administration of glycopyrrolate; M & G group = administration of midazolam and glycopyrrolate; G*T = group*time; Time 1 = before administration of midazolam or glycopyrrolate; Time 2 = immediately after induction of anesthesia; Time 3 = 1 hr after induction; Time 4 = 2 hr after induction; Time 5 = 3 hr after induction.

esthesia, heat redistribution and hypothermia (Matsukawa et al., 1995, 1997; Taylor et al., 1985). In addition, Matsukawa et al. (2001) reported that cholinergic inhibitors prevented midazolam-induced core hypothermia. However, the previous findings have not been clarified the relationship between intra-operative hypothermia, benzodiazepine and cholinergic inhibitors. The present study investigates the effect of premedication using benzodiazepine (midazolam) and cholinergic inhibitor (glycopyrrolate) on intra-operative body temperature for the 3 hr after the induction of general anesthesia in a small group of Korean patients undergoing abdominal surgery.

We observed a decrease in body temperature of 0.15°C 1 hr after administration in the group receiving glycopyrrolate alone, and a decrease of 0.18°C in patients receiving midazolam and glycopyrrolate. These findings are at variance with those of Matsukawa et al. (2001), who reported an increase in core temperature of 0.3°C in patients given a cholinergic inhibitor (atropine) alone, but a constant body temperature in patients given a combination of benzodiazepine (midazolam) and atropine. The authors concluded that the core temperature in patients who administered atropine did not change because the thermoregulatory effects of a benzodiazepine receptor and cholinergic inhibitors opposed each other.

The reason for the discrepancy in prior findings can be attributed to differences in measurement time. The ambient temperature (23-24°C) for their study was similar to the present study (23.3°C) and the study (23-24°C) of Park and Yoon (2007). As in the present study, Park and Yoon (2007) measured body temperature throughout the 3 hr after induction of general anesthesia, but Matsukawa et al. (2001) observed body temperature for only 30 min after induction. These measurements seem insufficient to conclude that midazolam or glycopyrrolate affects intra-operative body temperature. The present findings are consistent with the results of Park and Yoon (2007), who reported that core body temperature in all surgical patients who took midazolam and glycopyrrolate decreased by 0.1-0.3°C 1 hr after the co-administration of the drugs. According to the finding of the present and the findings of Park and Yoon (2007), cholinergic inhibitors seem not to prevent intra-operative hypothermia in surgical patients who was administered midazolam. Matsukawa et al. (2001) maintained that glycopyrrolate prevented intra-operative hypothermia in patients who was administered with midazolam.

The present findings also indicate that midazolam or glycopyrrolate similarly decreases intra-operative body temperature in the 3 hr after in-

duction of anesthesia. These findings are consistent with those of Matsukawa et al. (1997), Sato et al. (2009), but inconsistent with Toyota et al. (2004). While Toyota et al. (2004) maintained that premedication using midazolam increased slightly body temperature at 2 hr after induction of general anesthesia, Matsukawa et al. (1997) and Sato et al. (2009) reported that midazolam as premedication significantly decreased core temperature. However, the decrease of body temperature in these studies may not be solely attributable to midazolam in certain aspects. Firstly, the decrease of core temperature reported by Matsukawa et al. (1997) and Sato et al. (2009) may instead be attributed to the low ambient temperatures in their studies (21.8-22.1°C and 22.2-22.4°C, respectively), in contrast to the ambient temperature of 23.3°C in the present study. Secondly, Sato et al. (2009) did not include a comparison group of patients who were not administered midazolam and did not receive forced-air warming, which hinders the conclusion that core temperature is significantly decreased by administration of midazolam as premedication. Finally, Matsukawa et al. (1997) concluded that midazolam had decreased TMT 30 min after the administration of midazolam (0.025 mg kg⁻¹), despite the lack of a statistically significant difference in body temperature between one group administered midazolam and the other group not administered midazolam. In the latter study, 0.075 mg kg⁻¹ dose of midazolam seemed to produce intra-operative hypothermia. However, because midazolam was only administered to participants without a cholinergic inhibitor in the study of Toyota et al. (2004), the data of Matsukawa et al. (1997) and Toyota et al. (2004) cannot be directly compared. Nonetheless, a premedication dose of 0.04 mg kg⁻¹ of midazolam seems not to lead to a decreased intra-operative body temperature.

In the present study, patients who received a combination of midazolam and glycopyrrolate had a slightly lower core temperature (0.1-0.2°C) throughout the 3 hr after the induction of anesthesia than those who received glycopyrrolate alone, even though there was not a statistically significant difference ($p = .065$) between the two groups. The difference of pre-operative core body temperatures (36.95 and 36.82°C, respectively) might be attributable to intra-operative body temperature. Further studies concerning intra-operative hypothermia and administration of midazolam are needed.

While core body temperature in our study decreased by approximately 1.0°C during the first 2 hr after the induction of anesthesia, despite provision of intra-operative warming, Toyota et al. (2004) reported a decrease in body temperature 0.4°C. This phenomenon can be attributed

to difference in the type of surgery or ambient temperature of the surgical theatre. While Toyota et al. (2004) selected patients undergoing arthroscopic knee surgery as study participants, we used patients undergoing abdominal surgery. Abdominal surgery tends to carry a high risk of peri-operative hypothermia (Abelha, Castro, Neves, Landeiro, & Santos, 2005; Flores-Maldonado et al., 1997; Kongsayreepong et al., 2003). In addition, the ambient temperature of our study setting was lower by 1°C (23.3°C) compared to that (24.4-24.7°C) in the study of Toyota et al. (2004).

Incidence of hypothermia was 34%, 44%, and 60% at 1 hr, 2 hr, and 3 hr following induction of general anesthesia, despite the continuous provision of intra-operative warming using a circulating water mattress. We therefore need to take other measures to maintain a body temperature greater than 36°C during anesthesia. Of course, a low ambient temperature leads to a decrease in core temperature (Kongsayreepong et al., 2003). Although El-Gamal et al. (2000) proposed maintaining the ambient temperature of the operating room at 26°C to prevent intra-operative hypothermia, such an ambient temperature will make surgeons sweat and will lead to waste electricity. As an application of intravenous fluid warming or skin surface warming failed to maintain intra-operative body temperature over 36°C (Park and Yoon, 2007), we recommend the combined use of these two warming methods for prevention of intra-operative hypothermia in patients who undergo abdominal surgery lasting more than 2 hr. In addition, awareness of the complications arising from intra-operative hypothermia and a strict adherence to thermal monitoring can play an important role in prevention of peri-operative hypothermia.

The major limitation of this study is that it was not a clinical randomization trial, but was a prospective study, a condition imposed by the Institutional Review Board, due to ethical concerns associated with a randomized controlled trial. However, by matching age, gender, and ASA physical status, we ensured homogeneity of the demographic and physiological characteristics. Our findings therefore are applicable to the management of intra-operative hypothermia for patients undergoing abdominal surgery under general anesthesia.

CONCLUSION

We conclude that there is no difference in intra-operative body temperature between patients administered a combination of midazolam (0.04 mg kg⁻¹) and glycopyrrolate (0.1 mg), and those administered alone

glycopyrrolate (0.1 mg) alone during the 3h after the induction of general anesthesia. A cholinergic inhibitor (glycopyrrolate, 0.1 mg) therefore seems not to affect intra-operative body temperature of patients given a benzodiazepine (midazolam, 0.04 mg kg⁻¹), and not to increase body temperature in patients not given a benzodiazepine during the 3 hr after the induction of general anesthesia. Intra-operative warming therefore is needed to prevent hypothermia in surgical patients who receive pre-operative administration of midazolam and/or glycopyrrolate.

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