Lipid-Emulsion Propofol Less Attenuates the Regulation of Body Temperature than Micro-Emulsion Propofol or Sevoflurane in the Elderly

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Purpose: Anesthesia and surgery commonly cause hypothermia, and this caused by a combination of anesthetic-induced impairment of thermoregulatory control, a cold operation room environment and other factors that promote heat loss. All the general anesthetics markedly impair normal autonomic thermoregulatory control. The aim of this study is to evaluate the effect of two different types of propofol versus inhalation anesthetic on the body temperature. Materials and Methods: In this randomized controlled study, 36 patients scheduled for elective laparoscopic gastrectomy were allocated into three groups; group S (sevoflurane, n=12), group L (lipid-emulsion propofol, n=12) and group M (micro-emulsion propofol, n=12). Anesthesia was maintained with typical doses of the study drugs and all the groups received continuous remifentanil infusion. The body temperature was continuously monitored after the induction of general anesthesia until the end of surgery. Results: The body temperature was decreased in all the groups. The temperature gradient of each group (group S, group L and group M) at 180 minutes from induction of anesthesia was 2.5±0.6°C, 1.6±0.5°C and 2.3±0.6°C, respectively. The body temperature of group L was significantly higher than that of group S and group M at 30 minutes and 75 minute after induction of anesthesia, respectively. There were no temperature differences between group S and group M. Conclusion: The body temperature is maintained at a higher level in elderly patients anesthetized with lipid-emulsion propofol.

Key Words: Body temperature, hypothermia, lipid emulsion, propofol, aquafol

INTRODUCTION

Mild hypothermia during anesthesia can induce severe adverse outcomes such as wound infection and a prolonged hospital stay.1 Hypothermia causes a shift to the left in the oxy-hemoglobin saturation curve, and it increases the incidence of myocardial ischemia and postoperative angina.2 As hypothermic patients recover from the anesthetic, shivering may occur, resulting in an increase in O2 consumption and CO2 production. The duration of action of neuromuscular blockers is prolonged for patients in a hypothermic state. Furthermore, intra-operative hypother-
Anesthetics and Body Temperature in Elderly

MATERIALS AND METHODS

Thirty six patients with the American Society of Anesthesiologists physical status classification I or II and who were above the age of 65 years and who had undergone laparoscopic gastrectomy were enrolled in this study. All patients provided written informed consent after approved by the Institutional Review Board for Human Studies. Patients with obesity (body mass index >30), perioperative fever (temperature >38°C), hypo- or hyperthyroidism, a requirement for blood transfusion during surgery, those taking medications likely to alter thermoregulation and those showing a temperature below 33°C during surgery were excluded. The temperature of the operating room during the perioperative period was kept at a set average temperature of 24±0.6°C for all the cases.

After at least 8 hours of fasting, the participants were given midazolam 3.5 mg orally 30 minutes before the induction of anesthesia. When the patients arrived at the operating room, a noninvasive blood pressure monitor, electrocardiogram, pulse oximetry and a bispectral index monitor (BIS XP monitor A 2000, Aspect Medical System Inc., Natick, MA, USA) were attached.

Patients were divided randomly into three groups using an Microsoft Excel 2007 generated randomization table, and allocation concealment was ensured by placing each patient’s group allocation in a sequentially numbered sealed envelope. Patient enrolment was completed by a trained nurse. The patients were allocated to receive sevoflurane (group S, n=12), lipid-emulsion propofol (group L; Fresenius®; Fresenius-Kabi, Homburg, Germany, n=12) or micro-emulsion propofol (group M; Aquafol®; Daewon pharm, Seoul, Korea, n=12). Sevoflurane was used as a comparator. The sample size was calculated based on a preliminary examination with using the same protocol (each group, n=5), which reported that the fall of body temperature at 180 min after induction of anesthesia was 2.5°C (group S), 1.7°C (group L) and 2.3°C (group M). The expected standard deviation of each group was 0.6°C. Therefore, 12 patients were required in each group in order to have a power of 80% and a significance level (α)=0.05 with using one-way analysis of variance tests.

For inducing anesthesia, the target effect site remifentanil concentration of 3.0 ng/mL was administrated via a syringe pump (Orchestra®, Fresenius Vial SA, France, or PION TCI, Bionet, Korea) in all the groups. Minto, et al.’s pharmacokinetic model was used. After equilibration of the plasma and effect site remifentanil concentrations, 1% propofol (Ane-pol®, Hana Pharm. Co., Seoul, Korea; lipid-emulsion propofol) at 2 mg/kg was intravenously injected in all the patients. Immediately after the loss of consciousness and the eyelash reflex, mask ventilation was started with 5 L/min of O₂, and rocuronium at 0.6 mg/kg was administered. The

mia will significant affect the neuromuscular function, and this occurs independent of neuromuscular blocker.³ Because of these problems, the prevention and treatment of intra-operative hypothermia are important.

In the operation room, hypothermia results from a combination of anesthetic-induced impairment of thermoregulatory control, a cold operating room environment and factors that are unique to surgery and that promote excessive heat loss. Intentional manipulation of heat exchange (behavioral regulation) is the most powerful thermoregulatory effector. But anesthetized patients cannot activate behavioral responses, which leaves them to rely on autonomic mechanisms and external thermal management. Vasocostriction is the most consistently used autonomic effector mechanism.⁴ All the general anesthetics that have been tested markedly impair normal autonomic thermoregulatory control.⁵ Sevoflurane profoundly inhibits thermoregulation.⁶ Propofol also produces a marked and linear decrease in the vasoconstriction and shivering thresholds.⁷ But the previous studies with propofol did not consider its composition. Lipid-emulsion propofol and micro-emulsion propofol have different solvents. Propofol (2,6-diisopropylphenol) is a water-insoluble molecule that is available as an oil-in-water lipid emulsion with soybean oil.³ Micro-emulsion propofol is a colorless liquid containing 1% propofol and 8% polyethylene glycol 660 hydroxystearate (Solutol HS 15; BASF Company Ltd., Seoul, Korea) as a nonionic surfactant and 5% tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofurol; Roche, Basle, Switzerland) as a co-surfactantor. The patients were allocated to receive sevoflurane (group S, n=12), lipid-emulsion propofol (group L; Fresenius®; Fresenius-Kabi, Homburg, Germany, n=12) or micro-emulsion propofol (group M; Aquafol®; Daewon pharm, Seoul, Korea, n=12). Sevoflurane was used as a comparator. The sample size was calculated based on a preliminary examination with using the same protocol (each group, n=5), which reported that the fall of body temperature at 180 min after induction of anesthesia was 2.5°C (group S), 1.7°C (group L) and 2.3°C (group M). The expected standard deviation of each group was 0.6°C. Therefore, 12 patients were required in each group in order to have a power of 80% and a significance level (α)=0.05 with using one-way analysis of variance tests.

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anesthesia in all the groups was subsequently maintained with sevoflurane (1.5-2.5% end-tidal sevoflurane) in group S, and Fresofol and Aquafol (2.5-4.0 µg/mL) were used in group L and group M, respectively. The maintenance doses for the study drugs were adjusted to maintain a bispectral index score (BIS) between 40 and 60. Ventilation was controlled to maintain an end-tidal CO₂ near 35 mm Hg. After endotracheal intubation, an esophageal stethoscope with a temperature sensor (esophageal stethoscope 400 series, De-Royal industries inc., Powell, TN, USA) was placed in the mid-esophagus. The body temperatures were recorded just after tracheal intubation and then every 15 minutes up to 180 minutes after tracheal intubation. The mean arterial pressures, heart rate, peripheral oxygen saturation and BIS were also recorded. All the patients received only Hartmann solution (kept at room temperature: approximately 25°C) during the operation, and the amount of fluid per hour was calculated by dividing the total infused fluid by the total operation time at the end of the operation. Shivering was observed in the recovery room, and it was treated with an intravenous injection of meperidine 25 mg.

All the statistics were analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The statistical measurements are shown as the number of patients, the mean or the mean±SD in the tables and figures. The patients’ characteristics (age, body weight and height) were compared using one-way ANOVA, followed by the Scheffe post hoc test. Chi-square tests were conducted for the gender ratio and the incidence of shivering. Changes in the temperature, the mean arterial pressure and the heart rate from baseline were analyzed by the Kruskal-Wallis test, and the Mann-Whitney test was used for post hoc comparisons. *p values <0.05 were deemed statistically significant. The sample size was calculated with PASS 2008 (NCSS, Kaysville, Utah, USA).

**RESULTS**

Thirty six patients satisfying inclusion criteria were screened for this study. No patient was excluded from the study. Monitoring the temperature of all patients was performed without complications. There were no differences between groups in age, gender, weight and height (Table 1).

Fig. 1 shows that the values of body temperature at each

| Table 1. Demographic Characteristics                          | Group S (n=12) | Group L (n=12) | Group M (n=12) |
|---------------------------------------------------------------|---------------|---------------|---------------|
| Age (yr)                                                      | 69.7±3.6      | 67.6±2.2      | 69.4±4.3      |
| Gender (M/F)                                                 | 8/4           | 10/2          | 9/3           |
| Weight (kg)                                                  | 57.3±9.7      | 56.8±8.6      | 57.0±9.3      |
| Height (cm)                                                  | 158.3±9.3     | 162.1±6.3     | 159.6±8.5     |

Values are means±SD and the number of patients. There were no significant differences among the three groups. Group S, the sevoflurane group; Group L, the lipid-emulsion propofol group and Group M, the micro-emulsion propofol group.

![Graph](image-url)
Anesthetics and Body Temperature in Elderly

Yonsei Med J   http://www.eymj.org   Volume 53   Number 1   January 2012

201

time were significantly lower than that at baseline in all the
groups. There was no significant difference in the body
temperature between group S and group M. The body tempera-
ture in group L was significantly higher than that in group S
(36.1±0.3°C vs. 35.7±0.4°C, respectively, p=0.034) from
30 minutes after induction of anesthesia; from 75 minutes, the
temperature in group L was significantly higher than that in
group M (35.6±0.4°C vs. 35.1±0.5°C, respectively, p=0.03).
The mean arterial pressure and heart rate showed no signifi-
cant clinical differences between the groups (Fig. 2). In all
the patients, the SpO2 was properly maintained (96-100%) in
spite of the pneumoperitoneum. The BIS and EtCO2 during
the operations were subsequently sustained at 32-51 and 32-
38, respectively. The amount of infused intravenous fluids per
hour and the incidence of shivering in the recovery room were
also similar between the groups (Table 2).

DISCUSSION

The major finding of this study was that two different types
of propofol showed different degree of reduction of body
temperature during general anesthesia. Micro-emulsion
propofol did not show the same result of body temperature
reduction as that for the lipid-emulsion propofol. The mi-
cro-emulsion propofol reduction in temperature was instead
equal to sevoflurane. Lipid-emulsion propofol produces a
linear decrease in the vasoconstriction thresholds,7 and vol-
atile anesthetics decrease the cold-response thresholds in a
nonlinear fashion.12 Ikeda, et al.13 reported that the decrease
in the core temperature caused by redistribution of heat dur-
ing anesthetic induction depends on the type of anesthetic,
and the propofol-induced hypothermia is greater than that
for sevoflurane. But Iwata, et al.14 reported that there were
no differences between sevoflurane and propofol for the
temperature management during operations. However in
the current study, group L maintained a higher degree of
body temperature than that in group S and group M. Sessler15
announced that the volatile anesthetics inhibit vasoconstric-
tion and shivering less than propofol at low concentrations,
but more than propofol at the typical anesthetic doses. This
is in accord with the current study’s results. There are some
factors that may explain these disparities. First, the current
study was performed on elderly people (mean age: 68.5

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**Fig. 2.** This figure shows the mean arterial pressure (MAP) and heart rate (HR) during anesthesia. There are no significant differences between the groups. Group S: sevoflurane group, Group L: lipid-emulsion propofol group, Group M: micro-emulsion propofol group.

**Table 2.** Anesthetic Characteristics and the Incidence of Shivering in the Recovery Room

|                          | Group S (n=12) | Group L (n=12) | Group M (n=12) |
|--------------------------|---------------|---------------|---------------|
| Intraoperative BIS (mm Hg) | 44.4±4.5      | 41.6±9.9      | 44.2±6.8      |
| Intraoperative EtCO2 (mm Hg) | 35.0±3.2      | 34.1±2.7      | 34.7±3.6      |
| Infused fluid volume per hour (mL) | 690±72       | 685±72       | 690±61       |
| Shivering incidence | 3             | 2             | 2             |

BIS, bispectral index score; EtCO2, end-tidal CO2; Infused fluid volume per hour, the total amount of intravenously infused fluid (Hartmann solution) divided by the operation time.
Values are means±SD and the number of patients.
Group S, the sevoflurane group; Group L, the lipid-emulsion propofol group; Group M, the micro-emulsion propofol group.
This study has some limitations. First, only the esophageal temperature was checked. Peripheral vasodilation can be estimated with a two-point extremity skin temperature gradient. This could be helpful for making a distinction between vasodilation and metabolism, and further studies will be needed to conclusively demonstrate this. Second, 1% propofol was used as an induction anesthetic agent in all the groups. This is the unusual method when clinically performing total intravenous anesthesia. Even if 1% propofol was used in all the groups, it could have an influence on anesthetic-induced vasodilation. It has been reported that a brief period of vasodilation during anesthetic induction causes substantial redistribution of hypothermia that persists throughout surgery.

In summary, the current study demonstrated that lipid-emulsion propofol did not decrease the body temperature as much as micro-emulsion propofol and sevoflurane. This suggests that the solvent or carrier substances of propofol, rather than the ‘propofol (propofol molecule itself)’, may be the component responsible for substantial influence on thermoregulation. Further investigation is required to elucidate which components of the propofol have an influence on thermoregulation.
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