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Effect of intraoperative infusion of sufentanil versus remifentanil on postoperative shivering in Korea: a prospective, double-blinded, randomized control study

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Background/aim: The number of published papers that compare the incidence of sufentanil- and remifentanil-related postoperative shivering is insufficient. We investigated the incidence of postoperative shivering after total intravenous anesthesia with either sufentanil or remifentanil in patients who underwent elective surgery.

Materials and methods: Eighty-three patients, with a physical status classified as American Society of Anesthesiologists I or II, were randomly allocated to either the remifentanil–propofol (RP group, n = 40) or sufentanil–propofol (SP group, n = 43) group. The primary endpoint was the incidence of postoperative shivering 1 h after entering the recovery room. The secondary endpoints were intraoperative core temperatures of the esophagus and tympanic membrane at 30 min after the induction of anesthesia and at the end of surgery.

Results: The overall postoperative shivering incidence was not significantly different between the RP (15%) and SP (11.6%) groups (P = 0.651). The intraoperative temperatures and their changes (the temperature 30 min after induction minus that after surgery) as measured at the distal esophagus and tympanic membrane were not significantly different between the RP and SP groups.

Conclusion: The incidence of postoperative shivering related to sufentanil was less than that related to remifentanil, with no significant differences in the intraoperative core temperatures.

Key words: Postoperative period, remifentanil, shivering, sufentanil

1. Introduction

Postoperative shivering usually occurs as a type of thermoregulatory response toward hypothermia, but it also can develop as a result of postoperative muscle hyperactivity, occurring even when the body temperature is within normal limits (1). Postoperative shivering can contribute to an increase in oxygen consumption (up to 200% to 300%) and vascular resistance, resulting from vasoconstriction (2,3). Fatal complications such as myocardial infarction may eventually occur.

Because of their rapid onset and recovery profiles, opioids are commonly used to control the intraoperative hemodynamic changes, but they carry the risk of postoperative shivering (4,5). Even though it is reported that remifentanil is associated with an increased incidence of postoperative shivering (ranging from 20% to 70%) (4,6), there is still debate on whether remifentanil induces more postoperative shivering compared to other opioids (7–12). There are only a few reports on whether the incidence of sufentanil-related postoperative shivering is greater than that of remifentanil (4,6).

We hypothesized that the incidence of postoperative shivering would be lower in patients who received sufentanil rather than remifentanil. Therefore, we investigated the incidence of postoperative shivering after total intravenous anesthesia with either sufentanil or remifentanil as a primary endpoint, and the intraoperative core temperatures measured at the esophagus and tympanic membrane as secondary endpoints.

2. Materials and methods

This prospective, randomized, controlled, double-blinded study was approved by our Institutional Review Board and registered with the Clinical Research Information Service (CRIS, ref: KCT0001888). Written informed consent was obtained from all participants, a legal surrogate, or the parents or legal guardians of participants who were minors.

We enrolled 86 patients who were aged 20 to 65 years, had an American Society of Anesthesiologists (ASA) physical status classification of I or II, and were scheduled to undergo elective surgery under total intravenous

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anesthesia. We excluded the patients who refused study enrollment or had a neuromuscular disease, abnormal hepatic, renal, or thyroid function, severe respiratory suppression, brain lesions, or an allergy to the study drugs. We excluded the patients who had taken medications such as anticonvulsants, antidepressants, or opioids within 2 weeks of the study. We also excluded pregnant or breastfeeding women, or women who planned to get pregnant.

All patients were randomly allocated to either the remifentanil–propofol (RP group, n = 43) or sufentanil–propofol (SP group, n = 43) group using a random numbers table obtained via a computer program (Figure 1).

After premedication with intramuscular midazolam (0.05 mg kg^{-1}) 30 min prior to the induction of anesthesia, the participant was transported to the operating room. Prior to the induction of anesthesia, we recorded the temperature of the tympanic membrane. The induction and maintenance of anesthesia was performed with total intravenous anesthesia using propofol (3 μg mL^{-1}) and either remifentanil (4.0 ng mL^{-1}; RP group) or sufentanil (0.5 ng mL^{-1}; SP group) with a target-controlled infusion (TCI) pump (Orchestra; Fresenius Vial, Brezins, France) (13). After equilibration of the plasma and effect-site target concentrations of all intravenous hypnotics and opioids, we performed endotracheal intubation 1 min after the injection of rocuronium bromide (0.6 mg kg^{-1}) and inserted an esophageal stethoscope at the best audible site of heart sounds to record the esophageal temperatures. The concentration of the propofol infusion was adjusted to maintain the bispectral index score between 40 and 60. The concentrations of the remifentanil or sufentanil infusions were adjusted in order to maintain mean arterial pressure changes within ±20% during the maintenance of anesthesia. The settings of mechanical ventilation were also adjusted to maintain the $ETCO_2$ between 35 to 45 mmHg with a 50% oxygen–air mixture. Sustained hypotension (≤80 mmHg of systolic arterial pressure) and bradycardia (≤50 beat/min) were treated with intermittent bolus injections of ephedrine (10 mg) and atropine (0.5 mg), respectively. All patients were transferred to the recovery room, which was automatically temperature-controlled at 28 ± 2 °C, after recovery from the neuromuscular block with sugammadex (2 mg kg^{-1}) at the end of surgery. Each patient was routinely tucked under a blanket to maintain body temperature during the stay in the recovery room.

The patients and investigators were blinded to the study medications. A noninvestigating nurse loaded them into indistinguishable numbered syringes and randomized the medications using a random number table. Noninvestigating anesthesiologists controlled the concentration of the opioid infusions used for the induction and maintenance of anesthesia.

The primary endpoint was the incidence of postoperative shivering, which was evaluated using a table with a definition based on the degree of shivering in 4 steps at 1 h after entering the recovery room (5). A degree ≥1 was used as the cut-off value for significant postoperative shivering. In the case of 2 or more points of postoperative shivering, a forced-air warming device was applied. The secondary endpoints were the intraoperative core temperatures as measured at the esophagus (Teso) and tympanic membrane (Ttym), which were recorded 30 min after the induction of anesthesia and at the end of surgery. In addition, we calculated and recorded the intraoperative temperature changes (temperatures 30 min after induction minus those after surgery) in the esophagus (Δ Teso) and tympanic membrane (Δ Ttym). The demographic and intraoperative data (sex, ASA physical status, age, height, weight, operation type, operation time, anesthesia time, urine output, blood loss, intravenous fluid intake, infusion rate of remifentanil or sufentanil, and room temperature) were also recorded. Urine output (UO) was categorized into the 3 subgroups for analysis: 0 mL, 0 mL–500 mL, and ≥500 mL.

2.1. Statistical analysis

The necessary sample size was calculated by taking the level of statistical significance as $\alpha = 0.05$ and $\beta = 0.2$ using z-tests of G*Power software (v3.1.9.1) with different proportions of the incidences of postoperative shivering in the remifentanil (0.63) and alfentanil (0.325) groups, which were reported in Apitzsch's study (14). We required 42 patients in each group and enrolled 86 patients, assuming that the dropout rate would be 5%.

SPSS (Windows v21.0, IBM Corp., Armonk, NY, USA) was used for statistical analysis. All measured values are presented as either the mean ± SD, mean (95% confidence intervals [95% CI]), or number of patients (%).

The data on the incidence of postoperative shivering, sex, ASA physical status, operation type, and category of urine output were compared using the chi-square test. The data on age, height, operation time, anesthesia time, blood loss, intravenous fluid intake, and room temperatures were compared using Student's t-test. The data on intraoperative temperatures of the esophagus and tympanic membrane and their intraoperative changes were also compared using Student's t-test. $P < 0.05$ was considered to indicate statistical significance.

3. Results

Eighty-three patients were enrolled, because 3 patients in the RP group were excluded due to the cancellation of their surgery (2 patients) and an allocation failure (1 patient) (Figure 1).

There were no significant differences in the age, sex, height, weight, operation type, and ASA physical status between the RP and SP groups (Table 1).

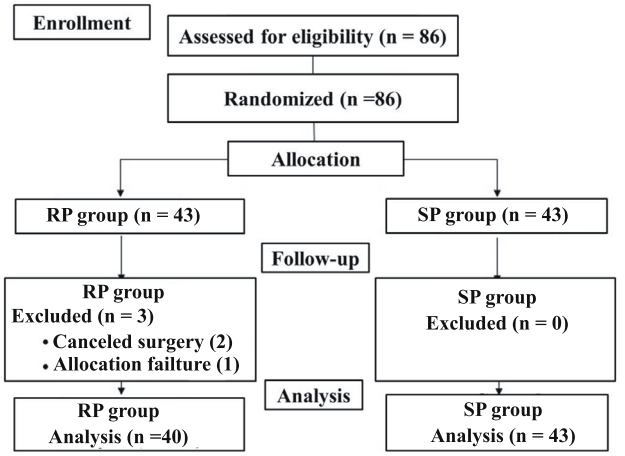

Figure 1. CONSORT Flow chart.

The postoperative shivering incidence was not significantly different between the RP and SP groups (Table 2, P = 0.694). The overall postoperative shivering incidence was not significantly different between the RP (15%) and SP groups (11.6%, P = 0.651; Table 2).

The intraoperative baseline tympanic membrane temperatures were not significantly different between the RP and SP groups (36.1 [36.0–36.2] °C vs. 36.2 [36.1–36.3] °C, respectively; P = 0.687) (Figure 2). The intraoperative tympanic membrane temperatures at the end of surgery were not significantly different between the RP and SP groups (35.8 °C [35.6–36 °C] vs. 35.7 °C [35.5–35.9 °C], respectively; P = 0.735) (Figure 2). Similarly, the intraoperative tympanic membrane temperature change (the temperature 30 min after induction minus that after surgery; ΔTtym) was not significantly different between the RP and SP groups (0.3 [0.2–0.4] °C vs. 0.4 [0.3–0.5] °C, respectively; P = 0.354) (Figure 2).

The intraoperative baseline distal esophageal temperatures were not significantly different between the RP and SP groups (35.9 [35.7–36.1] °C vs. 36.1 [35.9–36.3] °C, respectively; P = 0.234) (Figure 2). The intraoperative distal esophageal temperatures at the end of surgery were not significantly different between the RP and SP groups (35.6 [35.4–35.8] °C vs. 35.6 [35.4–35.8] °C, respectively; P = 0.692] (Figure 2). There was also no difference in the change in intraoperative distal esophagus temperature (ΔTeso) between the RP and SP groups (0.4 [0.3–0.5] °C vs. 0.4 [0.3–0.5] °C, respectively; P = 0.394) (Figure 2).

There were no significant differences in the intraoperative data including operation time, anesthesia time, urine output, blood loss, intravenous fluid intake, and room temperature between the RP and SP groups (Table 3).

4. Discussion

In the present study, the overall incidence of postoperative shivering in patients who received sufentanil (11.6%) was lower than that in patients who received remifentanil

Table 1. Patient characteristics.

	RP group (n = 40)	SP group (n = 43)	P value
Sex (M/F)	20/20	24/19	0.596
ASA physical status (I/II)	30/10	24/19	0.067
Age (years)	45.6 ± 11.6	47.4 ± 12.4	0.493
Height (cm)	166.1 ± 8.2	166.6 ± 8.1	0.758
Weight (kg)	68.4 ± 13	68.4 ± 10	0.986
Operation type			0.572
General surgery	7 (17.5)	5 (11.6)	
Gynecological surgery	1 (2.5)	2 (4.7)	
Oral and maxillofacial surgery	3 (7.5)	1 (2.3)	
Orthopedic surgery	11 (27.5)	6 (14.0)	
Otolaryngological surgery	6 (15.0)	10 (23.3)	
Plastic surgery	1 (2.5)	1 (2.3)	
Spine surgery	8 (20.0)	13 (30.2)	
Urologic surgery	3 (7.5)	5 (11.6)	

The values are expressed as mean ± SD or numbers of patients (n [%]). There are no significant differences between groups. ASA: American Society of Anesthesiologists. P < 0.05 was considered to indicate statistical significance.

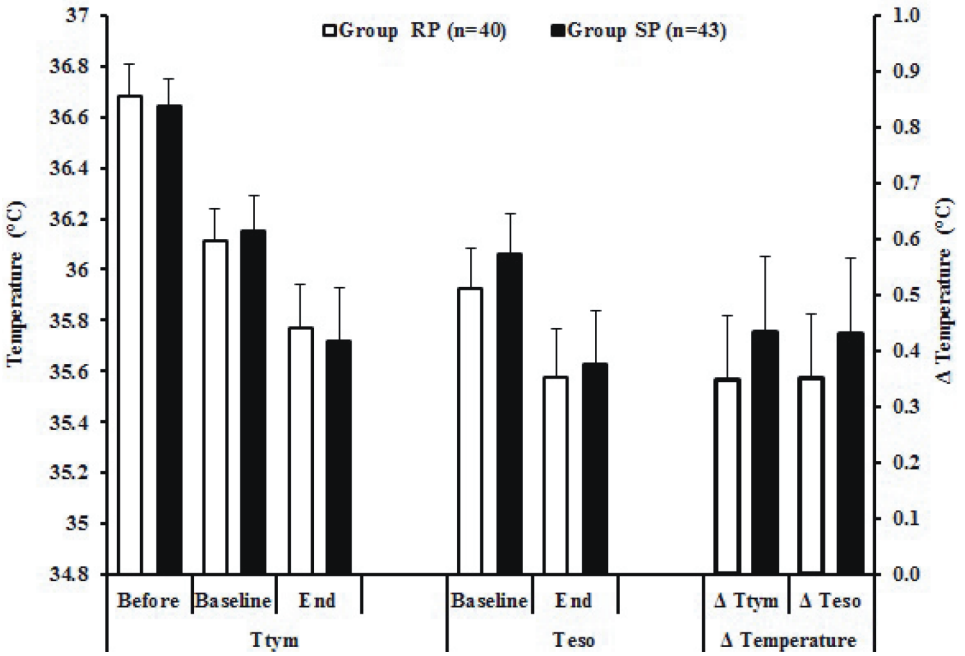

Figure 2. Intraoperative temperatures of distal esophagus and tympanic membrane (°C). There were no significant differences between the groups. Ttym: tympanic membrane temperature; Teso: distal esophageal temperature; Δ Temperature: temperature change (the temperature 30 min after induction minus that after surgery); Δ Ttym: tympanic membrane temperature change; Δ Teso: intraoperative distal esophagus temperature change; before: before induction; baseline: 30 min after induction; end: end of surgery. The values are expressed as mean (95% confidence intervals). $P < 0.05$ was considered to indicate statistical significance.

Table 2. Incidence and grade of postoperative shivering.

	RP group (n = 40)	SP group (n = 43)	P value
Overall incidence of postoperative shivering	6 (15)	5 (11.6)	0.651
Grade of postoperative shivering			0.694
0: No shivering	34 (85)	38 (88.4)	
1: Mild fasciculation of face or neck	2 (5)	2 (4.7)	
2: Visible tremor involving more than one muscular group	3 (7.5)	1 (2.3)	
3: Gross muscular activity involving the entire body	1 (2.5)	2 (4.7)	

The values are expressed as numbers of patients (n [%]). There were no significant differences between the groups. $P < 0.05$ was considered to indicate statistical significance.

(15%), with no significant difference in the intraoperative core temperatures. A meta-analysis showed that the incidence of postoperative shivering associated with remifentanil was similar to that of sufentanil, but higher than that of fentanyl and alfentanil (4,6).

Postoperative shivering incidence of remifentanil has been reported to increase according to increase in infusion rate. Postoperative shivering was significantly greater in patients who received high doses (0.25–0.3 μg kg^{-1} min^{-1}) of remifentanil than in those who received low doses (0.1 μg kg^{-1} min^{-1}) (5,15). Nakasuji et al. (15) also reported that high doses of remifentanil induced a higher incidence (60%) of postoperative shivering compared with low doses (20%). In our study, the mean infusion rate of remifentanil

Table 3. Intraoperative data.

	RP group (n = 40)	SP group (n = 43)	P value
IR of remifentanil (μg kg^{-1} min^{-1})	0.13 (0.11–0.15)		
IR of sufentanil (ng kg^{-1} min^{-1})		8.8 (8.1–9.5)	
Operation time (min)	142.1 (110.7–173.5)	129 (108.5–149.4)	0.480
Anesthesia time (min)	163.5 (131.2–195.8)	153.6 (132.7–174.5)	0.605
Urine output [UO; n (%)]			0.057
0 mL = UO	21 (52.5)	29 (67.4)	
0 mL < UO < 500 mL	12 (30)	13 (30.2)	
500 mL ≤ UO	7 (17.5)	1 (2.3)	
Blood loss (mL)	165.8 (53.1–278.4)	153.6 (59.1–128.1)	0.222
Intravenous fluid intake (L)	1.1 (0.7–1.4)	0.9 (0.7–1.0)	0.392
Troom, baseline (°C)	21.5 (21.1–21.8)	21.3 (21–21.6)	0.495
Troom, end (°C)	21.7 (31.3–22)	21.5 (21.2–21.9)	0.496

The values are expressed as mean (95% confidence intervals) or numbers of patients (n [%]). There were no significant differences between the groups. Baseline: at 30 min after induction; End: the end of surgery. IR: infusion rate. $P < 0.05$ was considered to indicate statistical significance.

was 0.13 μg kg^{-1} min^{-1}, which was defined as a low dose (5,15). Our study showed an overall 15% postoperative shivering incidence after infusion of remifentanil, which was similar to the results of Nakasuji's study (15).

Sufentanil linearly decreased the shivering threshold as the infusion rate increased (16). However, the incidence of postoperative shivering after the infusion of sufentanil had not been sufficiently evaluated. A meta-analysis reports that the postoperative shivering incidence of sufentanil was about 4.1% (4). Martorano et al. (11) reported that the incidence of postoperative shivering was 6.3% after the infusion of sufentanil at a rate of 5–40 ng kg^{-1} min^{-1}. In our study, the mean infusion rate of sufentanil was 8.8 ng kg^{-1} min^{-1}, and the overall incidence of postoperative shivering related to sufentanil was 11.6%.

Even though opioids have a less potent effect on thermoregulatory control than volatile or intravenous anesthetics, opioids impair thermoregulation via reduction in the threshold for vasoconstriction and shivering. There is an unchanged gain and maximum intensity of shivering with a linear function of plasma opioid concentration (17–19). Therefore, shivering might not occur during opioid administration because opioids, or other anesthetics administered simultaneously, suppress shivering (20). However, opioids may be the only drugs remaining that blunt the thermoregulatory reflexes in patients who are hypothermic postoperatively because the volatile anesthetics are quickly exhaled after anesthesia (17).

Postoperative shivering normally occurs when patients develop intraoperative hypothermia due to an impairment of central and peripheral thermoregulation by anesthesia (17). In our study, either remifentanil or sufentanil infusion led to the development of mild intraoperative hypothermia (above 35 °C) with nonsignificant differences at the end of surgery. This implies that both remifentanil and sufentanil equally influence the impairment of thermoregulation intraoperatively, and similar incidence of postoperative shivering may thus be expected as a consequence. In our study, remifentanil caused a higher incidence of postoperative shivering than sufentanil; however, this difference was not significant.

Even though we used the mean (95% CI) infusion rates of remifentanil (0.13 [0.11–0.15] μg kg^{-1} min^{-1}) and sufentanil (8.8 [8.1–9.5] ng kg^{-1} min^{-1}) (Table 3), as the potency of sufentanil is ten times that of remifentanil, these rates were close to being equivalent (21). There are several reasons why remifentanil may have caused an insignificantly higher incidence of postoperative shivering than the other opioids. We focus here on the complex thermoregulatory mechanisms via the NMDA receptor and opioid receptor, which may account for the occurrence of shivering (20).

First, the opioid's effect on the μ receptor plays a role in the inhibition of postoperative shivering by increasing the interthreshold range (22). The threshold temperature for postoperative shivering has a linear relationship with the plasma concentration of opioids, but the plasma concentration that allows for spontaneous breathing does not seem as potent as with other antishivering drugs, such as meperidine (22). Postoperative shivering might be a result of the sudden decrease in the suppression of shivering by the opioids due to a weak or vanishing interaction between the opioid and μ receptor (20). When compared to other opioids, remifentanil in particular is more rapidly metabolized by plasma esterase and cleared from the blood within minutes after stopping the infusion. Therefore, the abrupt withdrawal of remifentanil without providing effective analgesic may aggravate the postoperative pain in patients. This can cause postoperative shivering by nonthermoregulatory rhythmic muscular activity earlier and more intensely than with sufentanil, even when patients are normothermic and vasodilated (1,8,9,17,23,24). Sessler (17) also suggested that remifentanil does not have a residual opioid effect to blunt thermoregulatory responses to hypothermia; thus, the high incidence of shivering in patients who have received intraoperative remifentanil is not surprising compared to that of those who received the longer-acting opioids.

The second reason is the activation of the central glutamatergic system, such as N-methyl-d-aspartate (NMDA) receptors, by the opioids. Short-acting opioids such as remifentanil may cause an acute opioid tolerance and opioid-induced hyperalgesia, which is significantly correlated with an increased risk of postoperative shivering by increasing pain (5,17,25). This mechanism's significance can be supported by the results of some investigators who showed that the postoperative shivering associated with remifentanil was attenuated by the inhibition of the NMDA receptor using ketamine and tramadol (5,15,20). Interestingly, the NMDA receptor can be activated by glycine, which acts as an acidic buffer in the drug preparation of remifentanil (26,27). Kleckner and Dingledine (27) reported that intraoperative high-dose remifentanil has enough high-dose glycine to activate NMDA receptors, while low-dose remifentanil does not. Therefore, in our study, which used low-dose remifentanil, the incidence of postoperative shivering related to remifentanil was lower than that of studies by other investigators who used high-dose remifentanil (5,15). The effect of glycine does not explain postoperative shivering caused by other opioids, because glycine is not found in their preparation.

There are some limitations associated with the present study. First, to evaluate hypothermia in the patients, we used the tympanic membrane and distal esophageal temperatures at the end of surgery, instead of the postoperative core temperature during recovery. Second, we could not confirm that postoperative shivering is related to postoperative pain, opioid-induced hyperalgesia, or acute opioid tolerance, because we did not evaluate them during recovery.

In conclusion, sufentanil induced less postoperative shivering than remifentanil, even though equivalent doses of the opioids were infused, and the same degree of mild intraoperative hypothermia developed. In addition, we need to pay attention to complex thermoregulatory mechanisms via the NMDA receptor and opioid receptor, which may account for the occurrence of shivering.

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