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ORIGINAL ARTICLE

# Effect of palonosetron on postanesthetic shivering after propofol–remifentanil total intravenous anesthesia

**Youn Yi Jo · Hyun Jeong Kwak · Mi Geum Lee · Oh Kyung Lim**

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**Abstract**
*Purpose* The authors conducted a prospective, randomized, double-blind study to evaluate the anti-shivering efficacy of palonosetron for patients after gynecological laparoscopy under total intravenous propofol–remifentanil anesthesia.
*Methods* Sixty female patients were randomly assigned to one of two groups and administered palonosetron 0.075 mg (palonosetron group, $n = 30$) or the same volume of normal saline (control group, $n = 30$) immediately after anesthesia induction. Anesthesia was induced and maintained with propofol and remifentanil, using a target-controlled infusion device. Esophageal and index finger temperatures were measured immediately after anesthesia induction (baseline) and at 15-min intervals until the end of the surgery. Postanesthetic shivering and side effects were assessed in a postanesthetic care unit.
*Results* Incidence of shivering was comparable in the control and palonosetron groups (10/30 vs. 8/30, respectively, $P = 0.779$). No significant intergroup differences were observed between esophageal and index finger temperatures. Compared with baseline values, esophageal temperatures decreased immediately after pneumoperitoneum in the control group and from 30 min after pneumoperitoneum in the palonosetron group.
*Conclusion* Use of palonosetron (0.075 mg) did not reduce the incidence of postanesthetic shivering after gynecological laparoscopy under propofol–remifentanil anesthesia. Further study including other 5-$HT_3$ antagonists or male patients would elucidate the effect of palonosetron on shivering after propofol–remifentanil anesthesia.

**Keywords** Gynecological laparoscopy · Total intravenous anesthesia · Palonosetron · Postanesthetic shivering

Y. Y. Jo · H. J. Kwak (✉) · M. G. Lee
Department of Anesthesiology and Pain Medicine, Gachon University, Gil Medical Center, 1198 Guwol-dong, Namdong-gu, Incheon 405-760, Republic of Korea
e-mail: hyun615@gilhospital.com

O. K. Lim
Department of Rehabilitation Medicine, Gachon University, Gil Medical Center, Incheon, Republic of Korea

## Introduction

Postanesthetic shivering (PAS) is distressing side-event of general anesthesia which affects 5–65 % of patients [1]. In addition to causing discomfort and increasing surgical pain, profound shivering may induce a marked increase in oxygen consumption of up to 500 %, which increases stress on the cardiopulmonary system and increases intraocular and intracranial pressures [2, 3]. Propofol and remifentanil total intravenous anesthesia (TIVA) is a useful anesthetic technique for laparoscopy [4, 5], but it has been reported that incidence of PAS is almost twice as high for propofol–remifentanil TIVA as for volatile anesthesia [6]. Furthermore, an earlier study concluded that intraoperative remifentanil infusion increases the incidence of PAS [7].

Serotonin (5-hydroxytryptamine; 5-HT) is of major importance in neurotransmission and in the control of postanesthetic shivering [8, 9]. It has recently been suggested that 5-$HT_3$ antagonists, which are well known in the context of postoperative nausea and vomiting (PONV), could reduce the incidence of PAS after regional or volatile anaesthesia [10–12]. However, the effect of palonosetron (a new-generation 5-$HT_3$ antagonist) on PAS after propofol–

remifentanil TIVA has not been studied. Therefore, we conducted this prospective, randomized, double-blind study to evaluate the effects of palonosetron on body temperature and PAS for patients after gynecological laparoscopy under propofol–remifentanil TIVA.

## Methods

After obtaining approval from our institutional review board for the study protocol, we obtained written informed consent from all patients.

### Subjects

Sixty women of American Society of Anesthesiologists physical status I or II that were electively scheduled to undergo gynecological laparoscopy, were enrolled in this prospective randomized study. Patients with a body temperature above 37.5 °C, thyroid disease, or uncontrolled hypertension or diabetes mellitus, and those that underwent surgical conversion to an open procedure were excluded. Patients were randomly allocated to one of two groups before the induction of anesthesia by use of computer-generated random numbers. The members of one group were administered normal saline (1.5 ml; the control group, $n = 30$), whereas members of the other were administered i.v. palonosetron (0.075 mg; 1.5 ml; the palonosetron group, $n = 30$) immediately after anesthesia induction (Fig. 1).

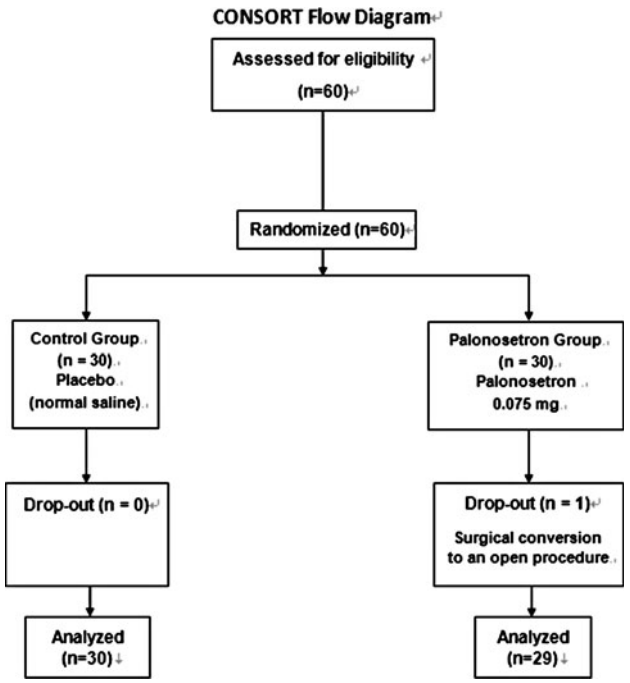


**Fig. 1** CONSORT flow diagram

### Anesthesia

Patients were premedicated with midazolam (0.04 mg/kg) intramuscularly 1 h before anesthetic induction. On arrival in the operating room, standard anesthetic monitors were attached. The same standard anesthetic regimen was used for all study subjects. Briefly, anesthesia was induced and maintained with propofol (target blood concentration 2.5–3.5 μg/ml) and remifentanil (target blood concentration 2.5–3.5 ng/ml), using a target-controlled infusion device (Orchestra; Fresenius Kabi, Bad Homburg, Germany). The pharmacokinetic sets used for calculation of target effect-site concentrations for propofol and remifentanil were Schnider's and Minto's pharmacokinetic models, respectively. Rocuronium 0.6 mg/kg was given to facilitate tracheal intubation. Lungs were ventilated at a tidal volume of 8–10 ml/kg, a respiratory rate of 8–14 breaths/min with no external positive end-expiratory pressure (PEEP), to maintain an end-tidal carbon dioxide concentration ($ETCO_2$) of 35–40 mmHg using 50 % oxygen/50 % medical air. Propofol and remifentanil concentrations were adjusted to maintain a bispectral index (BIS) score between 40 and 60. Heart rate (HR), mean arterial pressure (MAP), and $SaO_2$ were recorded pre-induction and at 5-min intervals immediately after anaesthesia induction until the end of the surgery. For patient-controlled analgesia, an infusion device (Accufuser®; Woo-young Meditech, Seoul, Korea) prefilled with fentanyl (800 μg) in a total volume of 100 ml was connected to an intravenous line after induction. The infusion device was programmed to deliver a basal infusion rate of 2 ml/h and an intermittent bolus dose of 0.5 ml/15 min.

### Operative procedures and monitoring

Esophageal temperature was measured and recorded as core temperature by use of an esophageal stethoscope with a temperature sensor (DeRoyal, Powell, TN, USA), and index finger temperature was recorded at the dorsum of the index finger on the hand, contralateral to the intravenous line, immediately after anesthesia induction (defined as baseline) and at 15-min intervals immediately after pneumoperitoneum until the end of the surgery. Temperatures were monitored and recorded using Datex-Ohmeda AS/3 modules (GE Healthcare, Helsinki, Finland). Room temperature was maintained at 24–25 °C, and when core temperature fell below 35.0 °C a warming mattress containing circulating water at 38 °C was applied. Administered fluids, laparoscopic irrigation fluid, and $CO_2$ gas were not warmed, and all patients were placed in the 15° Trendelenburg position after $CO_2$ insufflation. All operations were conducted by the same gynecologist using the same instruments. Pneumoperitoneum pressure was maintained at 15 mmHg.

### Evaluating body temperature and PAS

Tympanic temperature was also measured in the postanaesthetic care unit (PACU) by use of a tympanic thermometer (ThermoScan IRT 1020; Braun, Germany). PAS was documented visually by two anaesthesiologists and by two specified members of recovery room staff, who were unaware of group allocations. Shivering was classified as: grade 0, no shivering; grade 1, mild fasciculations of face or/and neck with ECG disturbances in the absence of voluntary arm activity; grade 2, visible tremors involving more than one group of muscles; grade 3, gross muscular activity involving the entire body and bed shaking [13]. In the PACU, a forced-air warmer (WarmTouch®; Mallinckrodt Medical, St Louis, MO, USA) was applied to patients with a tympanic temperature below 36 °C. Meperidine 25 mg i.v was administered when a patient had shivering grade 3 or requested rescue meperidine to control PAS. In the PACU, postoperative pain was assessed by use of the visual analog scale (VAS) score 30 min after entry. When the patient had moderate or severe pain (VAS >5) and requested the analgesics, 30 mg ketorolac i.v. was administered as the first-line treatment and 50 μg of fentanyl i.v. as the second-line treatment in the PACU.

### Statistical analysis

The primary outcome in this study was PAS incidence. We chose a PAS incidence of 57.5 %, as previously elsewhere [12]. To detect a difference in PAS incidence from 57.5 to 20 % in the treatment group, with a power of 80 % at an α-error of 0.05, we calculated that 26 patients per group would be required. Assuming a drop-out rate of approximately 20 %, we recruited 30 patients per group.

SPSS 17.0 (SPSS, Chicago, IL, USA) was used for data analysis. Data distributions were tested by use of the Kolmogorov–Smirnov test. Normally distributed continuous variables were compared by use of the independent *t* test or by repeated measures analysis of variance (ANOVA) with Bonferroni's correction. Values are expressed as means (SD) or numbers of patients; *P* values of <0.05 were considered statistically significant.

## Results

No significant differences were observed between the characteristics of patients, for example, age, gender, weight, height, previous medical history, and propofol and remifentanil infusions, in the palonosetron and control groups. Duration of anesthesia, surgery, and pneumoperitoneum were non-significantly different in the two groups (Table 1).

Incidence of PAS in the PACU is summarized in Table 2. Ten patients in the control group and 8 patients in the palonosetron group experienced shivering, and 5 in the control group and 4 in the palonosetron group received rescue meperidine to control PAS. No significant intergroup difference was found ($P = 0.779$). VAS score at 30 min (control group vs. palonosetron group; $4.2 \pm 2.1$ vs. $4.7 \pm 1.8$, $P = 0.382$) after entry in the PACU was similar between the groups. Rescue ketorolac was given to 2 in the control group and to 1 in the palonosetron group, and there was no significant difference.

The changes of body temperature are summarized in Fig. 2. No significant intergroup difference was observed for esophageal or index finger temperatures. However, esophageal temperature decreased significantly immediately after pneumoperitoneum in the control group but at 30 min after pneumoperitoneum in the palonosetron group. On the other hand, index finger temperature decreased

**Table 1** Patient characteristics

| | Control ($n = 30$) | Palonosetron ($n = 29$) |
|---|---|---|
| Age (years) | 45 (7) | 46 (4) |
| Medical illness (*n*) | | |
| Diabetes mellitus | 1 (3) | 1 (3) |
| Hypertension | 5 (17) | 3 (10) |
| Weight (kg) | 61 (9) | 63 (8) |
| Height (cm) | 160 (5) | 159 (5) |
| Anesthesia time (min) | 121 (38) | 114 (26) |
| Operation time (min) | 95 (26) | 96 (26) |
| Infused remifentanil (μg/min/kg) | 0.12 (0.04) | 0.12 (0.04) |
| Pneumoperitoneum time (min) | 71 (22) | 76 (27) |

Values are mean (SD) or number of patients (%)

**Table 2** Incidence of postanesthetic shivering and the requirement of a rescue meperidine

| | Control ($n = 30$) | Palonosetron ($n = 29$) |
|---|---|---|
| Tympanic temperature (°C) | 35.9 (0.5) | 36.1 (0.5) |
| Postanesthetic shivering | 10 (33) | 8 (27) |
| Grade 1 | 5 (17) | 2 (7) |
| Grade 2 | 2 (7) | 4 (14) |
| Grade 3 | 3 (10) | 2 (7) |
| Rescue meperidine (*n*) | 5 (17) | 4 (14) |

Values are mean (SD) or number of patients (%)

Grade 1, mild fasciculations of face or neck, ECG disturbances in the absence of voluntary activity of arms; Grade 2, visible tremors involving more than one group of muscles; Grade 3, gross muscular activity involving the entire body, bed shaking

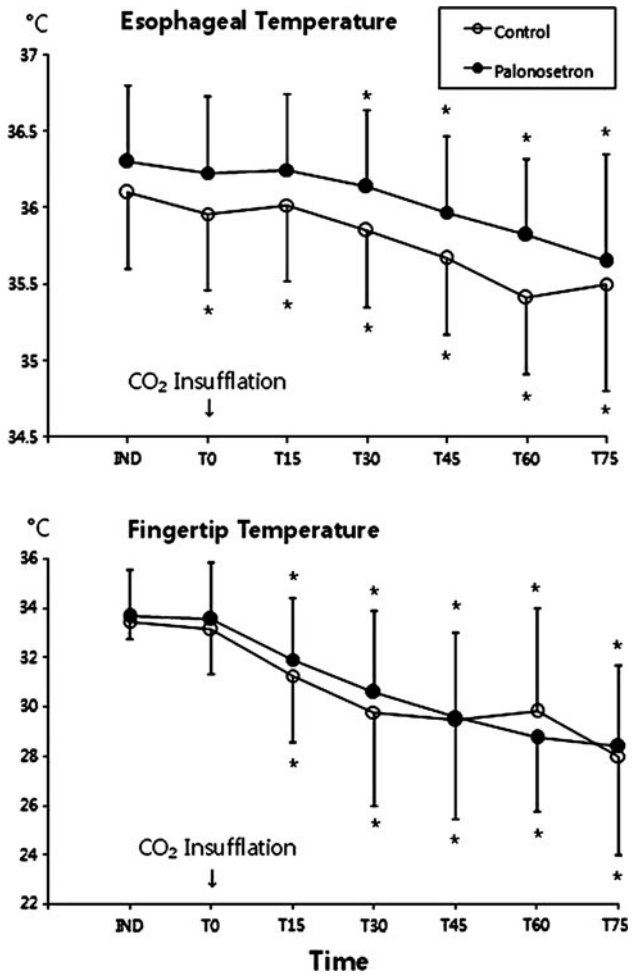


**Fig. 2** Changes of esophageal and index fingertip temperatures, at 15-min intervals, of patients undergoing gynecological laparoscopy. *Open circles*, indicate the control group; *filled circles*, the palonosetron group; *bars* show standard deviations; *IND*; immediately after anesthesia induction; *T0–T75*, from immediately to 75 min after pneumoperitoneum. *$P < 0.05$, vs. baseline values (IND) within the group

significantly 15 min after pneumoperitoneum in both groups.

No patient received a transfusion. Three in the control group suffered from PONV and required rescue antiemetics in the PACU, but no patient complained of PONV in the palonosetron group. None of the 60 study subjects experienced a postoperative myocardial problem, wound infection, or bleeding diathesis.

## Discussion

In this prospective, randomized, double-blind trial, i.v palonosetron (0.075 mg) failed to reduce the incidence of PAS after propofol–remifentanil TIVA in patients undergoing gynecological laparoscopy.

Although the etiology of PAS is not clearly understood, there is general agreement that it is a thermoregulatory phenomenon associated with hypothermia. During laparoscopic procedures, hypothermia has been reported to be caused primarily by insufflation of cold $CO_2$, irrigation with fluid at ambient temperature, and effects of the anesthetic agents [14, 15]. After general anesthesia, core hypothermia is largely the result of the core-to-peripheral redistribution of body heat, characterized by an $\sim$1 °C decrease in core temperature within the first 30 min after induction, followed by an increase in fingertip skin temperature [16, 17]. Furthermore, core temperatures are consistently lower during propofol anesthesia than during inhaled sevoflurane anaesthesia [16]. In this study, no difference was observed between core or fingertip skin temperatures in the control and palonosetron groups, which is in accord with the findings of a previous study conducted by Powel and Buggy [10], in which it was found that ondansetron does not affect the redistribution of hypothermia. Furthermore, it was suggested that the anti-shivering effect of ondansetron is independent of intraoperative hypothermia [10].

It has been suggested that 5-$HT_3$ receptor antagonists inhibit generalized thermoregulatory responses at the level of hypothalamus, which is primarily responsible for thermoregulatory control [18, 19]. Furthermore, the classic 5 $HT_3$ receptor antagonists ondansetron and granisetron have been reported to reduce the incidence and the severity of PAS after volatile or regional anesthesia [10–12]. However, a recent study by Browning et al. [20] reported that ondansetron 8 mg did not reduce the incidence and severity of PAS in obstetric patients undergoing cesarean section under combined spinal epidural anesthesia. They suggested that their negative findings might result from the characteristics of the study subjects, who were all pregnant, and the different mechanism of thermoregulatory shivering in pregnant woman [20]. In this study, administration of palonosetron (0.075 mg) immediately after anesthesia induction was also not effective at preventing PAS after propofol and remifentanil TIVA for gynecologic laparoscopy. This difference could be explained by different molecular structures and 5-$HT_3$ receptor interactions, because older drugs are based on a 3-substituted indole structure resembling serotonin whereas palonosetron has a fused tricyclic ring system attached to quinuclidine moiety. Accordingly, palonosetron interacts with 5-$HT_3$ receptors at sites different from or additional to those involved in ondansetron and granisetron binding [21].

Another possible explanation, which we consider important, is that PAS was caused by the intraoperative infusion of remifentanil rather than propofol. In a previous study, remifentanil-induced PAS was found to be a sign of opioid withdrawal associated with the use of short-acting

opioids rather than a symptom of intraoperative hypothermia [7]. In this previous study, it was demonstrated that PAS occurred more frequently after high-dose (0.25 μg/kg/min) than after low-dose (0.1 μg/kg/min) remifentanil infusion (60 vs. 20 %, $P = 0.009$), even though all patients in both groups had similar pain-free times (VAS = 0) in PACU; overall 31 % of patients experienced PAS and a mean infused dose of 0.12 μg/kg/min. These findings indicate that the underlying mechanism of remifentanil-induced PAS is acute opioid tolerance resulting in the stimulation of *N*-methyl-α-aspartate (NMDA) receptors, as occurs during hyperalgesia. Furthermore, this mechanism is supported by the findings of previous studies in which NMDA antagonists, for example ketamine and magnesium sulfate, were found to effectively reduce the incidence of PAS for patients undergoing propofol–remifentanil anesthesia [22, 23]. Thus, we believe that a single administration of palonosetron did not have a specific anti-shivering effect on remifentanil-induced PAS, because the underlying mode of action of palonosetron differs from that of hypothermia-induced PAS. Thus further studies including other 5 $HT_3$-antagonists, for example ondansetron and granisetron, could elucidate the anti-shivering efficacy of 5 $HT_3$-antagonists on PAS after propofol–remifentanil anesthesia.

Some limitations of this study require consideration. In particular, an arbitrary dose of palonosetron (0.075 mg) was used because of a lack of previous studies indicating the dose required to control PAS and of the lack of a dose–response study to determine the minimum effective dose of palonosetron. Accordingly, because ondansetron could produce a dose-dependent reduction in PAS after isoflurane anesthesia that is significant at larger doses [10], larger doses of palonosetron might have prevented PAS. We used palonosetron at 0.075 mg, because it has been reported to have a better antiemetic effect than ondansetron at 8 mg [16], which according to a previous study reduced the incidence of shivering from 57 to 15 % [10]. In addition, it is possible that 5-$HT_3$ antagonists have an effect in reducing PAS after propofol–remifentanil anesthesia, but our study had insufficient power to detect it, which is another limitation in our study. However, based on the results of our study, any such anti-shivering effect would be so small as to be clinically unimportant and insufficient to justify prophylactic use of palonosetron for patients undergoing gynecologic laparoscopy under propofol–remifentanil anesthesia.

In summary, a single administration of palonosetron at 0.075 mg during anesthesia induction failed to prevent PAS after propofol–remifentanil anaesthesia or affect core-to-peripheral heat redistribution in patients undergoing gynecological laparoscopy. Our results show that palonosetron at this dosage does not reduce PAS, which provides a possible explanation for the ineffectiveness of 5-$HT_3$ antagonists at preventing PAS related to remifentanil-induced acute tolerance mediated by the NMDA receptor.

**Conflict of interest** No external funding was provided for this study, and the authors have no competing interests to declare.

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