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# Evaluation of Postoperative Shivering With Remifentanil-Propofol Intravenous Anesthesia in Ambulatory Gynecologic Procedures: The Relationship With Intraoperative Core Body Temperature

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**Abstract**

**Objectives:** Postanesthesia shivering (PAS) is a frequent side effect of general anesthesia and one of the leading causes of patients' discomfort after recovery from anesthesia, especially in an ambulatory setting. Remifentanil is reported to have an increased incidence of PAS compared to other analgesics maybe due to several ways that are unrelated to the patient's core body temperature variations. The aim of this study was to evaluate the effects of remifentanil versus fentanyl on postoperative shivering and its relationship with intraoperative hypothermia.

**Materials and Methods:** Accordingly, 100 patients scheduled for outpatient gynecologic procedures were studied in two randomly assigned groups. All patients received total intravenous anesthesia for induction and maintenance with remifentanil-propofol and fentanyl-propofol in remifentanil and fentanyl groups, respectively. The incidence and severity of shivering, as well as core body temperature, hemodynamic variations, and probable postoperative complications were evaluated and recorded based on the aim of the study.

**Results:** Based on the results, there were no significant differences in demographic data. On the other hand, the incidence and severity of shivering were significantly higher in the remifentanil group compared to the fentanyl group ($P<0.001$) although core body temperatures did not differ between the two groups ($P>0.05$). Finally, no significant difference was observed in hemodynamic changes and other postoperative complications between the two groups ($P>0.05$).

**Conclusions:** In general, remifentanil is a very short-acting and safe opioid for ambulatory procedures. However, it is associated with a higher incidence and severity of shivering as compared to other opioids unrelated to intraoperative hypothermia. Thus it must be noted that some strategies are needed to prevent this complication.

**Keywords:** Post-anesthetic shivering, Remifentanil, Fentanyl, Propofol

## Introduction

Inevitable hypothermia is referred to lowering in central temperature below 36°C and mostly occurs during general anesthesia due to different factors including the direct inhibition of body temperature control with anesthetic agents, a decrease in metabolism, body exposure to operating room cold temperature, and heat loss from surgical sites (1). Postanesthesia shivering (PAS) is an involuntary movement that affects one muscle group or more and generally occurs in the early recovery phase after general anesthesia. According to studies, its incidence is in the range of 6.3%-60% (average 40%). Mild perioperative hypothermia does not necessarily occur before the appearance of post anesthetic shivering but it encourages this phenomenon and more serious the hypothermia leads to the higher the probability of postanesthetic shivering (2). In addition, shivering is a potentially serious complication that increases oxygen consumption roughly 100% in proportion to intraoperative heat loss. Further, postoperative shivering possibly aggravates wound pain by stretching incisions. The most important determinants of shivering risk are young age and low core temperature (1).

Nowadays, most gynecologic procedures are performed on an outpatient basis. Furthermore, the rapid recovery and shorting of hospital stay need improved ambulatory service quality and low medical fees, and the technique of anesthesia is one of the most important determinant factors in the patient's rapid recovery. Ideal anesthesia in outpatient procedures is the one with rapid and smooth induction, an optimal surgical condition, and rapid recovery with the least complications like postoperative pain, shivering, and nausea-vomiting. Thus, the basic requirement for anesthetic care is to provide optimal safety,

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quality, and cost-efficacy (3). The current use of total intravenous anesthesia (TIVA) for ambulatory surgery seems to be abundant. It is encouraged by the simplicity of the method, increased experience, and declining costs with a combination of propofol and remifentanil (4).

Remifentanil is a short-acting, highly potent, selective μ-opioid which is associated with predictable and rapid recovery. However, it seems that in comparison with other opioids such as fentanyl, PAS is high after the discontinuance of remifentanil. A number of studies have also reported the increased incidence of PAS with remifentanil administration but the results and its underlying mechanism are highly conflicting (5-17). The mechanisms underlying PAS include acute opioid tolerance of short-acting narcotics, which is closely related to the activation of the N-methyl-d-aspartate receptor in the perception of pain and hyperalgesia with remifentanil (12-17). Therefore, this study aimed to evaluate the incidence and severity of post-anesthesia shivering with remifentanil versus fentanyl administration during outpatient gynecologic procedures, and its relation to intraoperative hypothermia during TIVA with these two anesthesia techniques.

## Materials and Methods

In this double-blind randomized clinical trial, after approval of the Ethics Committee of Tabriz University of Medical Sciences, written informed consent forms for the operation were obtained from 110 patients with the American Society of Anesthesiology (ASA) physical status I or II, who were scheduled for ambulatory gynecologic procedures including hysteroscopy, diagnostic laparoscopy, and transvaginal oocyte retrieval (ovarian puncture) under total intravenous anesthesia in Alzahra teaching hospital (from February 2014 to February 2015). In a previous study, the response within each subject group was normally distributed with a standard deviation of 9.2. If the true difference in the experimental and control means is 5.3, we need to study 48 experimental and 48 control subjects in order to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) of 0.8. To allow for potential dropouts, it was decided to recruit 55 patients per group. The type I error probability associated with this test of null hypothesis is 0.05. The exclusion criteria included patients with ASA class III or higher, those with cardiopulmonary diseases, preoperative fever, and the use of any antipyretic or anti-inflammatory medication and any surgery time longer than 2 hours. After arrival to the operating room, patients were randomly assigned to one of the two groups of 55 according to a table of random numbers using a computer-generated randomization list to receive remifentanil-propofol or fentanyl-propofol as total intravenous anesthesia. Moreover, basic vital signs (i.e., arterial blood pressure, heart rate, and Sao2) and core body tympanic membrane temperature (with an aural canal thermometer: Albors Patient Care Unit B5-SNTI/E2/M/C, Saadat Medical Equipment Producer and Supp, Masimo Set Code: ALT9204) were measured and recorded for all patients. Additionally, the room temperature was adjusted at 22-24°C, and all patients received 500-1000 mL of crystalloid before the induction of anesthesia. In addition, the temperature of all administered fluids was equal to that of the operating rooms. General anesthesia was induced with midazolam 0/05 mg/kg IV and propofol 2-2.5 mg/kg IV, followed by the infusion of propofol 5-10 μg/kg/h in both groups. In the remifentanil group (group R) remifentanil 1 μg/kg IV was administered for induction and infused in the range of 0.1-0.25 μg/kg/h for anesthesia maintenance. In the fentanyl group (group F), fentanyl 1 μg/kg IV was administered for induction and repeated as needed for anesthesia maintenance in order to keep the depth of anesthesia according to the patient's heart rate and blood pressure variations. Any increase in the heart rate or blood pressure in the range of 20% suggested the need for fentanyl administration or adjustment of remifentanil infusion. Similarly, patients' vital signs and core body temperatures were recorded throughout surgery at certain intervals. In the operating room, all patients were covered with operation drapes and one cotton blanket in the recovery room. After the surgery, patients were evaluated for the signs and severity of shivering according to Wrench five-point rating score (0 = 'No shivering', 1='Peripheral vasoconstriction without visible muscular activity', 2 = 'Visible muscular activity confined to one muscle group', 3 = 'Visible muscular activity in more than one muscle group', and 4 = 'Gross muscular activity involving the entire body') with a recovery nurse, who was blunted to the opioids, in both groups. Further, any other probable complications were controlled and recorded, including the occurrence of pain, nausea-vomiting, agitation, and hemodynamic instability. Furthermore, the low scores of shivering (1 or 2) were treated with additional warming and blanket, and high scores (3 or 4) were controlled with 25-30 mg intravenous meperidine. All data were analyzed using an independent *t* test for quantitative variables, and Fisher exact probability and chi-square tests were applied for qualitative variables. Moreover, the Mann-Whitney U test was performed for non-parametric variables between the groups and repeated measures to compare variables during times within the groups. The analysis was performed using SPSS software, version 16.0. Statistical results were considered significant when $P < 0.05$.

## Results

A total of 110 patients were assigned in this double-blind randomized clinical trial study and randomly allocated to two groups of 55 to receive the standard total intravenous anesthesia with remifentanil-propofol or fentanyl–propofol infusion during surgery. Nonetheless, 5 patients

in each group were excluded from the study according to the consort flow chart, and finally, 50 patients were analyzed in each group. There were no differences in patient's characteristics such as ages, weights, ASA physical status, and duration and type of operation (Table 1).

Hemodynamic changes including systolic and diastolic blood pressures, heart rate, and arterial O2 saturation ($SaO_2$) were evaluated and recorded as a basis after the induction of anesthesia, at 5th, 10th, and the end of the surgery (Table 2). There were no significant differences in terms of the above-mentioned parameters between the two groups ($P > 0.05$).

The incidence and severity of postanesthetic shivering (PAS) were assessed in both groups. PAS was significantly higher in the group receiving remifentanil compared to the fentanyl group ($P < 0.001$). Additionally, the severity of PAS was greater in patients who received remifentanil as compared to those in the fentanyl group. Therefore more patients in the remifentanil group were administered meperidine (25 mg IV) as rescue treatment for severe shivering (scores 3 or 4), the details of which are presented in Table 3.

Core body temperature using an aural canal thermometer was measured at different times and compared between the groups. Based on the results, core temperature decreased by the induction of anesthesia and during the operation in both fentanyl and remifentanil groups ($P < 0.001$, $P < 0.001$, respectively). However, there were no significant differences in core temperatures at different times between the two groups (Table 3). Likewise, the incidence of any other postoperative complication (e.g., nausea vomiting and pain) demonstrated no significant differences between the groups (Table 4). Eventually, patients in the remifentanil group experienced more agitation compared to those who received fentanyl.

## Discussion

This study compared the effects of remifentanil-propofol and fentanyl-propofol on postanesthetic shivering in ambulatory gynecologic procedures and the results revealed that the incidence and severity of shivering were higher in patients receiving remifentanil-propofol when compared to the other group who received fentanyl-propofol. On the other hand, although core body temperature decreased during the surgery and anesthesia, both groups showed no difference in core temperatures. Accordingly, the increase in the incidence and severity of PAS with remifentanil is attributed to a mechanism

**Table 1.** Demographic characteristics of patients

| Patients (N=100) | Group R (n= 50) | Group F (n= 50) | *P* Value |
|---|---|---|---|
| Age (year), mean (SD) | 37.86 (7.81) | 32.36 (7.05) | 0.16 |
| Weight (kg), mean (SD) | 69.54 (7.07) | 67.96 (8.45) | 0.31 |
| ASA, No. (%) | | | |
| I | 38 (76%) | 38 (76%) | 1 |
| II | 12 (24%) | 12 (24%) | |
| Operation time (min), mean (SD) | 31.1 (12.8) | 36.2 (11.45) | 0.75 |
| Type of operation, No. (%) | | | |
| Hysteroscopy | 25 (50%) | 44 (44%) | |
| Ovarian puncture | 18 (36%) | 39 (39%) | 0.45 |
| Diagnostic laparoscopy | 7 (14%) | 17 (17%) | |

Note. ASA: American Society of Anesthesiology; SD: Standard deviation.

**Table 2.** Hemodynamic and Core Temperature Variations During the Surgery and Postoperative Complications in the 2 Groups at Different Times

| Patients (N=100) | Group R (n=50) | Group F (n=50) | *P* Value |
|---|---|---|---|
| | Mean (SD) | Mean (SD) | |
| Systolic BP | | | |
| Basic | 123.8 (14.5) | 121.5 (13.9) | 0.91 |
| After induction | 119.4 (14.4) | 119.4 (15.6) | |
| 5th minute | 117.3 (12.05) | 119.46 (14.9) | |
| 10th minute | 115.6 (18.6) | 117.5 (13.2) | |
| End of operation | 119.3 (11.06) | 118.1 (12.7) | |
| Diastolic BP | | | |
| Basic | 77.9 (11.5) | 74.8 (12.8) | 0.67 |
| After induction | 74.9 (12.2) | 71.3 (12.9) | |
| 5th minute | 74.0 (11.9) | 71.0 (13.5) | |
| 10thminute | 73.8 (11.27) | 70. 2 (12.1) | |
| End of operation | 74.9 (11.2) | 68.8 (12.2) | |
| Body temperature/°C | | | |
| Basic | 36.2 (0.3) | 36.4 (0.45) | 0.64 |
| After induction | 36.1 (0.35) | 36.2 (0.44) | |
| 5th minute | 35.8 (0.41) | 35.9 (0.4) | |
| 10thminute | 35.4 (0.41) | 35.7 (0.43) | |
| End of operation | 35.3 (0.42) | 35.4 (0.51) | |

Note. BP: Blood pressure; SD: Standard deviation.

**Table 3.** Frequency and Severity of PAS in 2 Groups

| Shivering Score | Group R (n=50) | Group F (n=50) | *P* Value |
|---|---|---|---|
| 0 | 12 (24%) | 32 (64%0 | <0.001 |
| 1 | 10 (20%) | 15 (30%) | <0.001 |
| 2 | 10 (20%) | 2 (4%) | <0.001 |
| 3 | 10 (20%) | 1 (2%) | <0.001 |
| 4 | 8 (16%) | 0 (0%) | <0.001 |
| Meperidine additional | 18 (36%) | 1 (2%) | <0.001 |

Note. PAS: Postanesthesia shivering.

**Table 4**. Postoperative Complications in 2 Groups at Different Times

| Patient (N = 100) | Group R (n = 50) | Group F (n = 50) | *P* Value |
|---|---|---|---|
| | No. (%) | No. (%) | |
| Nausea-vomiting | 3 (6) | 4 (8) | 0.50 |
| Pain | 7 (14.0) | 5 (10.0) | 0.38 |
| Agitation | 11 (22.0) | 5 (10.0) | 0.08 |

other than lowing in core body temperature, which was observed with many agents.

Gynecologic procedures like hysteroscopy, laparoscopy, and ovarian puncture are performed as an outpatient basis, but all these procedures are painful and require the use of sedative and analgesic agents to achieve patient intra and postoperative analgesia and safe discharge of patients without any complication. To reach these purposes, the most commonly used agents for these ambulatory procedures are propofol and remifentanil because of their rapid onset, easy titration, and rapid offset (3-5). On the other hand, some of the postoperative complications are observed by using intraoperative opioids like remifentanil, fentanyl, and alfentanil. These complications include shivering, nausea, vomiting, pruritus, respiratory depression, and hemodynamic instability. However, remifentanil administration was reported to have higher incidences of postoperative hyperalgesia and higher PAS compared to other opioids (3-11).

The results of the present study showed that the incidence of shivering is higher in patients who received a remifentanil-propofol infusion in comparison with patients receiving intravenous fentanyl-propofol as total intravenous anesthesia. In addition, the severity of shivering according to the five-point rating scale was higher in the remifentanil group compared to the fentanyl group, and more patients in this group required additional medication for the treatment of shivering in the post-anesthesia care unit. Core body temperatures before anesthesia and at different times during the surgery were evaluated as well. In both groups, core temperature decreased from the beginning to the end of the surgery about 0.5-1.5°C, as is generally observed in patients undergoing general anesthesia. Contrarily, this drop in core temperature was observed in both groups and the groups did not differ in this regard. Accordingly, the reason for PAS with remifentanil cannot be attributed to intraoperative occurred hypothermia, as is found with other opioids. All opioids inhibit thermoregulatory responses, thus shivering does not occur during the surgery since the threshold of shivering decreases below body temperature. On the other hand, it is possible that the threshold return to normal immediately after the discontinuation of remifentanil be due to the unique kinetics of the drug. Shivering triggers when the threshold increases faster than the increase in body temperature during recovery from general anesthesia. Another explanation is that shivering is a sign of opioid withdrawal caused by acute intolerance. Short-acting opioids like remifentanil could cause acute opioid tolerance and hyperalgesia via the stimulation of N-Methyl-d-aspartate (NMDA) receptors. Therefore patients receiving remifentanil, especially in high doses were sensitive to shivering after sudden discontinuation (5,12-19).

Nakasuji et al studied the effect of high-dose (0.25 μg/kg/min) versus low-dose (0.1 μg/kg/min) remifentanil in postoperative shivering and concluded that shivering was more frequent by using high-dose infusions presumably due to the activation of NMDA receptors (7). In our study, a range of 0.2-0.3 μg/kg/min was used and the infusion rate was titrated according to hemodynamic signs in order to achieve the adequate depth of anesthesia, which resulted in the high incidence and severity of shivering in this group.

Based on the findings of our study, there were no significant differences between the groups regarding core body temperatures although patients' core body temperatures gradually decreased throughout the surgery in both groups. Nakasuji et al also found no differences in rectal and palm temperatures in patients who received remifentanil (7). Similarly, Komatsu et al evaluated all remifentanil effects in a systematic review and then compared it with other short-acting opioids and represented more postoperative shivering in about 85 trials (18). Likewise, Röhm et al compared total intravenous anesthesia with propofol and remifentanil with desflurane-fentanyl anesthesia without any difference in body temperature (19).

Further, Oka et al assessed factors leading to postoperative shivering in patients undergoing laparoscopic colectomy with remifentanil and concluded that the duration of surgery and the concentration of opioid plasma are possibly more important than core body temperature for the occurrence of PAS (20). However, Naito et al compared postoperative shivering and pain in patients undergoing laparoscopic surgery and demonstrated that shivering was higher in the remifentanil group compared to the fentanyl group. They further found that body temperature was also lower in the remifentanil group (21), which contradicts the findings of our study and the two above-mentioned studies.

In this study, blood pressure was evaluated in both groups. Arterial blood pressures varied during the surgery at different times (i.e., immediately after, 5th minute, 10th minute, and at the end of the operation) within each group but there were no significant differences in blood pressure changes between the two groups. In another study, Ozkose et al compared recovery profiles including hemodynamic in two groups who received remifentanil versus alfentanil-based TIVA and reported that arterial pressure decreased more severely 1after the induction of anesthesia with remifentanil compared to alfentanil (17). However, Komatsu et al demonstrated that remifentanil is associated with more hypotension and bradycardia than other opioids (18). Other postoperative complications were evaluated in this study as well. Although no difference was found in postoperative pain, nausea vomiting, patients in the remifentanil group were more anxious than the fentanyl group. Finally, Möllhoff et al compared the efficacy and safety of remifentanil and fentanyl in fast track coronary

artery bypass graft and concluded that the overall adverse effects such as shivering, pain, and hypotension were greater in the remifentanil group (22).

## Conclusions

Based on these results, although the total intravenous anesthesia with remifentanil is a safe anesthetic technique according to stable intraoperative hemodynamic, its use can increase postoperative shivering as compared with other opioids including fentanyl. Intraoperative body temperature does not correlate with remifentanil-induced PAS. Therefore, the higher incidence of PAS with remifentanil probably reflects the mechanism of acute opioid tolerance and the stimulation of N-methyl-d-aspartate receptors as observed with remifentanil induced hyperalgesia. Thus, patients receiving remifentanil throughout a procedure are sensitive to shivering after sudden discontinuation.

This study has some limitations regarding the accurate evaluation of PAS during transport from the recovery room to the ward. Eventually, although the ambient temperature was constant, environmental changes could have developed and influenced PAS.

## Conflict of Interests

Authors have no conflict of interests.

## Ethical Issues

The study was approved by the Ethics Committee of Tabriz University of Medical Sciences (Ethics number IR.TBZMED.REC.1395.414 ).

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