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# Effect of Low Dose Remifentanil on Postoperative Pain Relief and Heart Rate Variability in Post-Anaesthesia Care Unit

## Anestezi Sonrası Bakım Ünitesinde Düşük Dozda Remifentanilin Postoperatif Ağrıyı Gidermede ve Kalp Atım Hızı Değişkenliği Üzerindeki Etkisi

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Abstract / Öz

**Objective:** Several reports have shown the negligible adverse effects of low-dose remifentanil on the autonomic nervous system. We propose that the administration of low-dose remifentanil would be beneficial without adverse respiratory and hemodynamic effects. This study aimed to examine the effects of low-dose remifentanil on postoperative pain relief and heart rate variability (HRV) after surgery.

**Methods:** In total, 20 patients, who underwent breast cancer surgery, were analysed for HRV in the post-anaesthesia care unit (PACU). A sedative dose of remifentanil was continuously infused if patients experienced pain while in PACU. The remifentanil infusion dose was determined by achieving analgesia with no adverse effects on hemodynamics and/or respiration. Variables of low-frequency power, high-frequency power and low-frequency power/high-frequency power ratio were measured before and after the administration of remifentanil. Pain score was expressed as the numeric rating scale (NRS) from 0 to10.

**Results:** The mean dosage of remifentanil administered as a continuous infusion was 0.029±0.0042 μg $kg^{-1}$ $min^{-1}$. After remifentanil administration, the value of the NRS decreased from 4.2±2.9 to 2.7±2.6. In addition, the value of high-frequency power increased from 35.6±14.3 to 49.4±3.0.

**Conclusion:** The continuous infusion of low-dose remifentanil may reduce post-operative pain scores and trigger the relative activation of the parasympathetic nervous system in post-surgical patients. This indicates that continuous infusion of low-dose remifentanil may be a useful option for postoperative pain relief in cases where postoperative pain control proves inadequate even with the application of regional block technique.

**Keywords:** Heart rate variability, remifentanil, after surgery, low dose

**Amaç:** Bazı raporlarda düşük doz remifentanilin otonom sinir sistemi üzerindeki önemsiz yan etkileri gösterilmektedir. Düşük doz remifentanil uygulamasının solunumsal ve hemodinamik yan etkileri olmaksızın daha faydalı olacağını düşünmekteyiz. Bu çalışmanın amacı düşük doz remifentanilin postoperatif ağrının giderilmesi ve kalp atım hızı değişkenliği (HRV) üzerindeki etkilerini incelemektir.

**Yöntemler:** Meme kanseri ameliyatı geçiren toplam 20 hasta anestezi sonrası bakım ünitesinde (PACU) HRV açısından analiz edildi. Hastalar PACU'de iken ağrıları olduğunda sedatif dozda remifentanil sürekli olarak uygulandı. Remifentanil infüzyon dozu, hemodinamikler ve/veya respirasyon üzerinde herhangi bir yan etkisi olmayan analjeziye ulaşılmasıyla belirlendi. Düşük frekans gücü, yüksek frekans gücü ve düşük frekans gücü/yüksek frekans gücü oranı değişkenleri remifentanil uygulamasından önce ve sonra ölçüldü. Ağrı skoru sayısal derecelendirme ölçeği (NRS) ile 0 ve 10 değerleri arasında gösterildi.

**Bulgular:** Sürekli bir infüzyon şeklinde uygulanan ortalama remifentanil dozajı 0,029±0,0042 μg $kg^{-1}$ $dk^{-1}$ idi. Remifentanil uygulaması sonrası, NRS değerinin 4,2±2,9'dan 2,7±2,6'ya düştüğü görüldü. Ayrıca, yüksek frekans gücü değeri 35,6±14,3'ten 49,4±3,0'a yükseldi.

**Sonuç:** Düşük doz remifentanilin sürekli infüzyonu, postoperatif ağrı skorlarını düşürebilir ve ameliyat sonrası hastalarda parasempatik sinir sisteminin rölatif aktivasyonunu tetikleyebilir. Bu da göstermektedir ki, düşük doz remifentanilin sürekli infüzyonu, postoperatif ağrı kontrolünün rejyonal blok tekniğinin uygulanmasıyla bile yetersiz kaldığı vakalarda postoperatif ağrının giderilmesinde faydalı bir seçenek olabilir.

**Anahtar Sözcükler:** atım hızı değişkenliği, remifentanil, ameliyat sonrası, düşük doz

## Introduction

The measurement of heart rate variability (HRV) is a non-invasive method for assessing the activities of the sympathetic and parasympathetic nervous system (1). There have been many reports examining the effects of anaesthetic agents or opioids on HRV (2-4). To ensure stable hemodynamics during anaesthesia, it is important to understand the effects of anaesthetic agents and opioids when measuring HRV.



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Komatsu et al. (2) demonstrated the differential effects of ketamine and midazolam on HRV. Fujiwara et al. (3) showed that spinal anaesthesia induced a decrease of both sympathetic and parasympathetic nerve activities. Several reports describe the effects of opioids on the activity of the sympathetic or parasympathetic nervous system (4-8). Carter et al. (4) examined the effects of morphine on sympathetic nerve activity in humans and found that the intravenous injection of morphine increased sympathetic nerve activity. Tirel et al. (5) investigated the effects of remifentanil on HRV in children who were administered sevoflurane anaesthesia at one minimum alveolar concentration (MAC), and reported that remifentanil (administered as a continuous infusion of 0.25 μg $kg^{-1}$ $min^{-1}$ for 10 min, then increased to 0.5 μg $kg^{-1}$ $min^{-1}$) reduced the inter-beat (RR) interval, but had little effect on parasympathetic nerve activity.

Noseir et al. (8) showed that sedative doses of remifentanil (at target concentrations of 2 and 4 ng $mL^{-1}$) resulted in analgesia, but did not affect neuro-circulatory vascular tone in young volunteers. This study led us to hypothesize that the administration of low-dose remifentanil may be useful for addressing postoperative pain. There have been some reports examining the effects of low-dose remifentanil for postoperative pain relief (9-12). Bowdle et al. (9) showed that continuous infusion of remifentanil at 0.05-0.15 μg $kg^{-1}$ $min^{-1}$ (a relatively high dose) could provide postoperative pain relief, but at the cost of frequent adverse respiratory events. By contrast, continuous infusion of relatively lower doses of remifentanil (0.02-0.05 μg $kg^{-1}$ $min^{-1}$) was not associated with adverse respiratory events, but was not able to reduce postoperative pain (11-12). We propose that low-dose remifentanil may be useful in providing postoperative analgesia without adverse respiratory and hemodynamic effects, as an additional analgesic modality to regional techniques such as the pectoral compartment block.

It is well known that anaesthetic doses of remifentanil (0.1-0.5 μg $kg^{-1}$ $min^{-1}$) result in increased parasympathetic nerve activity and depress respiration. However, there have been few reports describing the effects of low-dose remifentanil on both sympathetic and parasympathetic nerve activities following surgery.

The primary purpose of this study was to examine the effects of low-dose remifentanil on postoperative pain relief in the post-anaesthesia care unit (PACU); the secondary purpose was to examine the effects of low-dose remifentanil on sympathetic and parasympathetic nerve activities by assessing HRV.

## Methods

Study protocols were approved by the ethics committee of the Gunma Cancer Center. Written, informed consent was obtained from all patients prior to participation [University Hospital Medical Information Network (UMIN) Clinical Trials Registry UMIN000023285].

We analysed data from all 82 patients who underwent breast cancer surgery between 2015 and 2016 at Gunma Cancer Center. Of these 82 patients, we retrospectively selected 13 patients (Group B) who experienced relatively moderate pain [a numerical rating scale (NRS) score above 3] after surgery and who needed analgesic agents upon arrival at PACU. These patients received a single dose of a non-steroidal anti-inflammatory drug (NSAID; flurbiprofen axetil, 50 mg) for analgesia on admission to PACU. We also selected a control group composed of 7 age-matched patients who had no pain (an NRS value of 0 or 1) and no need for analgesic agents at PACU (Group A).

From the total, 12 patients were excluded because of inadequate HRV data (noise interference impeding HRV assessment due to postoperative shivering). Patients were also excluded from the study if they were elderly (above 70 years), had a history of cerebrovascular disease, ischemic heart disease, were treated with beta-blockers or had chronic obstructive lung disease, psychiatric illness and/or active liver disease (defined as glutamine oxaloacetate transaminase or glutamine pyruvate transaminase levels above 50 U $dL^{-1}$). After exclusion, we were able to analyse 20 out of the 82 patients; this included 7 control patients.

General anaesthesia was induced with 2 mg $kg^{-1}$ propofol, 1.0 mg $kg^{-1}$ rocuronium, and 0.2-0.5 μg $kg^{-1}$ $min^{-1}$ remifentanil, followed by endotracheal intubation. Muscle relaxation was achieved by intermittent administration of rocuronium. All patients were ventilated with 50% oxygen and 50% nitrogen using continuous monitoring of end-tidal carbon dioxide. Anaesthesia was maintained with a combination of 1.0%-2.0% sevoflurane in 50% oxygen and 50% nitrogen and intravenous remifentanil infused at a rate of 0.2-0.4 μg $kg^{-1}$ $min^{-1}$. To ensure appropriate intraoperative hemodynamics, the sevoflurane concentration was adjusted by the anaesthesiologist as needed.

Following surgery and before emergence from anaesthesia, PECS was performed in the operating room (ultrasound-guided infiltration of 20 mL 0.375% ropivacaine into the interfascial plane, between the pectoralis major and minor muscles) (13).

All patients were transferred to PACU. Immediately after patients received a dose of NSAID, anaesthesiologists analysed the NRS from 0 to10. If the NRS was above 3,

a sedative dose of remifentanil was continuously infused if patients complained of pain. The remifentanil infusion dose was determined by the attending anaesthesiologist to achieve appropriate analgesia without adverse effects on hemodynamics, defined as hypotension (systolic blood pressure below 80 mmHg) and bradycardia (heart rate below 50 beats per minute) or respiratory depression (such as a decreased respiratory rate below 6 breaths per minute). An initial dose of remifentanil was not administered owing to concerns about adverse effects (such as respiratory depression, hypotension and/or bradycardia). NRS was re-assessed in patients treated with remifentanil 1 hour after commencement of the infusion.

**Measurement of HRV**

Data were analysed for HRV using fast Fourier transform (Check My Heart$^{R}$, Daily Care Bio Medical Inc., Taiwan) (1).

Spectral analysis of the electrocardiogram makes it possible to show the relationship between parasympathetic and sympathetic nerve tones in different clinical situations. It has been shown that the peak of the high-frequency (HF) component reflects parasympathetic nerve activity, whereas the peak of low-frequency (LF) component depends on the balance of the sympathetic and parasympathetic nerve tones (1).

Heart rate variability was recorded at 5 minutes after admission to PACU and 1 hour after commencement of the remifentanil infusion, and the data was stored in a computer. According a previous report (1), the parameters of HRV were estimated in the classic frequency bands of low-frequency power (LF: 0.04-0.15 Hz), high-frequency power (HF: 0.15-0.45 Hz) and LF/HF ratio in PACU. The anaesthesiologists who analysed HRV data in the two groups were blinded with respect to the infusion of remifentanil.

**Statistical analysis**

All data were expressed as mean±standard deviation (SD). Unpaired t-tests or paired t-tests were used for analysing comparisons between groups. Statistical significance was set at $p<0.05$.

After completion of the study, we evaluated the sample size. In a previous study, Bowdle et al. (9) showed that administration of remifentanil (0.05-0.15 μg $kg^{-1}$ $min^{-1}$) could reduce the pain score from 3 to 0 or 1. Thus, we hypothesized that the NRS of 1-2 in group B was larger than that in group A. The sample size provided 80% power to detect a 20% difference between groups with a 5% probability of a type I error. All calculations were performed electronically using Stat View software version 5.0 (Abacus Concepts, Berkeley, CA) in Microsoft Windows 7.

Table 1. Demographic data

| | Group A | Group B | p |
|---|---|---|---|
| Number (n) | 7 | 13 | |
| Age (year) | 59±7 | 60±11 | 0.710 |
| Height (cm) | 154.9±4.9- | 150.5±4.7 | 0.065 |
| Weight (kg) | 52.7±7.7 | 48.9±3.1 | 0.213 |
| Aesthetic time (min) | 100±18 | 100±37 | 0.993 |
| Operation time (min) | 53±20 | 72±34 | 0.137 |
| Remifentanil use during surgery (mg) | 0.484±0.157 | 0.554±0.296 | 0.496 |
| Sevoflurane use during surgery (mL) | 30±6 | 38±14 | 0.114 |
| Fluid balance during surgery (mL) | 721±184 | 753±233 | 0.760 |
| Blood loss during surgery (mL) | 26±17 | 36±26 | 0.324 |

Group A: 7 patients without use of remifentanil in post-anaesthesia care unit (PACU)
Group B: 13 patients with use of remifentanil in PACU
Data are expressed as means±SD.

Table 2. High-frequency power, low-frequency power/low-frequency power and numerical rating scale in the two groups in post-anaesthesia care unit

| | Group A | Group B | p |
|---|---|---|---|
| HF | 36.1±9.0 | 35.6±14.3 | 0.933 |
| LF/LF | 1.9±0.8 | 2.3±1.4 | 0.476 |
| NRS | 0.6±0.8 | 4.2±2.9* | 0.0007 |

*p<0.05 compared to group A. Data are expressed as means±SD.
LF: low- frequency power; HF: high-frequency power; NRS: numerical rating scale

Table 3. High-frequency power, low-frequency power/low-frequency power and numerical rating scale before and after in Group B in post-anaesthesia care unit

| | Before remifentanil infusion | After remifentanil infusion | p |
|---|---|---|---|
| HF | 35.6±14.3 | 49.4±3.0* | 0.01 |
| LF/LF | 2.3±1.4 | 1.6±1.4 | 0.104 |
| NRS | 4.2±2.9 | 2.7±2.6* | 0.012 |

*p<0.05 compared to the point prior to remifentanil infusion. Data are expressed as means±SD.
LF: low-frequency power; HF: high-frequency power; NRS: numerical rating scale

## Results

Table 1 shows the demographic data of the two groups. There were no significant differences in age, height, weight, anaesthetic time or operation time between the two groups.

Table 2 shows HF and LF of the two groups. There were no significant differences in HF and LF/HF between the two groups. The NRS in group A was lower than that in group B.

Table 3 shows the HF and LF of group B before and after remifentanil administration. The mean dosage of continuous infusion of remifentanil was 0.029±0.0042 μg $kg^{-1}$ $min^{-1}$. After the administration of remifentanil, NRS value decreased from 4.2±2.9 to 2.7±2.6. In addition, the value of HF increased from 35.6±14.3 to 49.4±3.0.

## Discussion

The present study shows that the administration of low-dose remifentanil could increase HF in addition to reducing pain scores. Until now, only a few reports have shown the effects of anaesthetic agents on autonomic nervous system activity or HRV. Komatsu et al. (2) examined the effects of ketamine and midazolam on HRV and showed that ketamine induced sympathetic nerve activation while midazolam suppressed it. Hanss et al. (14) showed that spinal anaesthesia could result in decreased sympathetic nerve activity and a relative increase in parasympathetic nerve activity. These reports indicate the benefits of assessing the effects of anaesthetic agents on HRV to manage hemodynamics effectively during anaesthesia.

Opioids are known to affect sympathetic nerve activity. Carter et al. (4) showed that morphine increased resting muscle sympathetic nerve activity in healthy volunteers. A few reports have described the effects of remifentanil on HRV or autonomic nervous activity. Noseir et al. (8) examined the effects of an intravenous sedative dose of remifentanil on sympathetic outflow. They selected remifentanil effect-site target plasma concentrations of 2 ng $mL^{-1}$ and 4 ng $mL^{-1}$ because these dosages did not result in hypotension. They showed that a sedative dose of remifentanil resulted in analgesia, but no changes in muscle sympathetic nerve activity.

Tirel et al. (5) examined the effects of remifentanil on HRV in children under 1 MAC of sevoflurane anaesthesia, and found that although remifentanil provoked bradycardia, this was not related to the activation of the parasympathetic nervous system. In contrast, Shinohara et al. (7) showed that renal sympathetic nerve activity in rabbits was increased after a bolus injection of remifentanil.

In our study, an increased HF value, thought to reflect parasympathetic nerve activity, was found after the administration of low-dose remifentanil. This may indicate that low-dose remifentanil induces parasympathetic nerve activation without adverse hemodynamic or respiratory effects. This is partly inconsistent with previous reports, where remifentanil did not trigger the activation of the parasympathetic nervous system (5-8). This difference may be partly attributable to the clinical presentation and demographics of the patients studied; the subjects for the study by Tirel et al. (5) were children whereas our study subjects were adults. The differing methods of remifentanil infusion may also have affected the results.

Wujtewicz et al. (6) investigated a bolus dose of remifentanil whereas we employed a continuous infusion method. Noseir et al. (8) studied awake subjects whereas Tirel et al. (5) investigated subjects under 1 MAC of sevoflurane anaesthesia. It is well known that anaesthesia modulates sympathetic and parasympathetic nerve activities. Also, in this study, HRV was measured postoperatively. It is possible that surgical stress and pain could modulate the balance of sympathetic and parasympathetic nerve activities following surgery. Indeed, following administration of remifentanil, pain scores decreased to half the values prior to infusion. It is well known that pain provokes sympathetic nerve activity. In this study, we surmised that decreased pain may induce relative parasympathetic nerve activity.

Until now, there have been few reports examining the effects of low-dose remifentanil on postoperative pain control (9-12). Bowdle et al. (9) examined the effects of remifentanil (0.05-0.15 μg $kg^{-1}$ $min^{-1}$) on postoperative analgesia, and showed that pain scores were 0 or 1 in 64% of patients who received remifentanil. However, respiratory adverse events (oxygen saturation below 90% or respiratory rate below 12 breaths per minute) affected 29% of patients, in addition to a 35% incidence of nausea.

Subsequently, Calderón et al. (10) showed that 0.1 μg $kg^{-1}$ $min^{-1}$ was an effective alternative in the treatment of postoperative pain relief whereas 0.05 μg $kg^{-1}$ $min^{-1}$ was not. These reports demonstrated the efficacy of continuous remifentanil infusion (0.0-0.15 μg $kg^{-1}$ $min^{-1}$) on postoperative pain relief, although high-dose related adverse effects (respiratory depression or nausea and vomiting) were observed. In contrast, adverse effects were not observed with the use of low-dose remifentanil (0.02-0.05 μg $kg^{-1}$ $min^{-1}$), although this dose did not provide significant postoperative analgesia (11, 12).

We proposed that low-dose remifentanil, in addition to regional blockade, could provide postoperative pain relief without adverse effects because a previous study by Naga-

saka et al. (12) demonstrated this possibility. Our study revealed that low-dose remifentanil provided adequate postoperative analgesia without inducing adverse effects when pain control was inadequate with the presence of regional blockade.

Immediately after the end of surgery and before emergence from anaesthesia, NSAIDs were administered and PECS was performed for postoperative analgesia. Where postoperative analgesia was inadequate, a sedative dose of remifentanil was administered. Low-dose remifentanil was able to provide adequate pain relief without adverse hemodynamic or respiratory effects or exaggeration of parasympathetic nerve activity. The clinical implication of this study is that low-dose remifentanil is useful for achieving postoperative analgesia without adverse hemodynamic or respiratory effects.

### Study limitations

In this study, we only measured the effect of a single dose of remifentanil on HRV to avoid hemodynamic and respiratory depression. As such, the effects of subsequent doses of remifentanil on HRV still need to be examined. Additionally, we examined the effect of remifentanil on HRV postoperatively. In most cases, remifentanil is used intraoperatively; thus, the effect of remifentanil on HRV during surgery also needs to be examined.

In this study, PECS was performed on all patients for pain relief. As such the possibility exists that the regional blockade also exerts effects on the balance between sympathetic and parasympathetic nerve tones.

## Conclusion

Following surgery, continuous infusion of low-dose remifentanil could reduce the post-operative pain scores and trigger the relative activation of the parasympathetic nervous system. Our study indicates that continuous infusion of low-dose remifentanil, when pain control is inadequate despite the presence of regional blockade, may be a useful method for achieving effective postoperative analgesia without adverse effects.

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**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Gunma Cancer Center.

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