Effects of two methods of fentanyl bolus administration during remifentanil-based anesthesia on pain in the immediate postoperative period

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Abstract

Objective. To determine which method provides superior pain relief and recovery from anesthesia while minimizing adverse effects in the immediate postoperative period.

Methods. We studied 70 patients undergoing gynecologic laparotomy. Anesthesia was induced with propofol and remifentanil. After tracheal intubation facilitated with vecuronium or rocuronium, anesthesia was maintained with sevoflurane and remifentanil. Patients were randomly assigned to receive 8 µg/kg of fentanyl at the start of surgery (early-bolus group) or 6 µg/kg of fentanyl at 60 min before the anticipated end of surgery (late-bolus group). At the end of surgery, the times from discontinuation of sevoflurane until patient response to verbal commands and until extubation were recorded as indicators of recovery from anesthesia. Hemodynamic parameters, pain score, sedation grade, and incidence of side effects were evaluated at 0, 5, 10, 15, and 30 min after entering the post-anesthesia care unit (PACU).

Results. A longer recovery time from anesthesia was required in the late-bolus group compared with the early-bolus group, whereas mean pain score was significantly lower in the late-bolus group compared with the early-bolus group. Furthermore, mean dose of fentanyl administered in the PACU was significantly higher in the early-bolus group compared with the late-bolus group. Sedation grade and incidence of adverse effects were similar between the groups.

Conclusion. Administration of 6 µg/kg fentanyl at 60 min before the anticipated end of surgery during remifentanil-based anesthesia provided superior postoperative analgesia in the immediate postoperative period as compared with 8 µg/kg fentanyl administered at the start of surgery.

Keywords

Postoperative analgesia; Remifentanil; Fentanyl; Pain

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INTRODUCTION

Remifentanyl possesses the pharmacokinetic characteristic of a short context-sensitive half-time, and it can be administered at high doses right until skin closure with little risk of delayed postoperative recovery or respiratory depression¹⁾. However, this characteristic can result in severe pain in the immediate postoperative period if an adequate analgesic regimen is not initiated during surgery²⁾. Several methods exist for postoperative pain management including the continuation of the remifentanyl infusion and administration of longer-acting opioids during surgery²⁾. Although postoperative remifentanyl infusion can provide effective pain management, the high incidence of respiratory depression associated with its use is problematic³⁾. Morphine is also effective for pain management. However, when administered close to the end of surgery, its sedative effect sometimes results in delayed recovery from anesthesia⁴⁾.

Fentanyl is one of the commonly used drugs for pain control during and after surgery under remifentanyl-based anesthesia. Its long context-sensitive half-time is optimal for postoperative analgesia⁵⁾. Claxton *et al.* demonstrated that fentanyl causes less nausea and vomiting than equipotent doses of morphine⁶⁾.

In Japan, remifentanyl has been widely used for intraoperative analgesia since it became commercially available in 2007. However, no studies have demonstrated the most effective regimen for postoperative analgesia. The optimal dose and timing of intraoperative fentanyl administration under remifentanyl-based anesthesia necessary to achieve adequate pain relief with minimal risks of delayed recovery from anesthesia and postoperative respiratory depression also remain unclear.

In this study, we compared two regimens of fentanyl bolus administration to determine the appropriate timing of administration. A bolus dose of fentanyl was administered at either the start of surgery or 60 min before the anticipated end of surgery. The objective of this study was to determine which method of bolus fentanyl administration provides better pain relief and recovery from anesthesia, with less adverse effects in the immediate postoperative period.

PATIENTS AND METHODS

The study protocol was approved by the human ethics committee of Takasaki General Medical Center, and written informed consent was obtained from each patient. Seventy unpremedicated women scheduled for gynecologic laparotomy that was expected to last at least 90 min were included in this prospective, randomized study. All patients were American Society of Anesthesiologists (ASA) physical status I or II and between 20 and 70 years of age.

Patients with uncontrolled diseases such as arrhythmias, asthma, chronic use of opioid or use of opioid within 12 h before surgery, obesity (body mass index > 30 kg/m²), liver dysfunction, allergy to opioids or any other drug used in the study, psychiatric disorders, or alcohol dependence were excluded from the study. Patients in whom the surgery did not last for at least 90 min were also excluded.

In the operating room, routine monitoring of non-invasive blood pressure (NIBP), electrocardiogram, and pulse oximetry were initiated. General anesthesia was induced with 2 mg/kg propofol and 0.4 µg/kg/min remifentanyl. Muscle relaxation was achieved with 0.1 mg/kg vecuro-

nium or 0.6 mg/kg rocuronium and tracheal intubation was performed. Patients were ventilated using O₂/air (25%/75%). Anesthesia was maintained with sevoflurane at an inhaled concentration of 1.5% until the end of surgery. The remifentanyl infusion rate was adjusted to maintain intraoperative blood pressure within 20% of the value measured on arrival at the operating room. Hypotension was treated with an intravenous bolus dose of ephedrine.

Randomization was based on computer-generated codes maintained in sequentially numbered, opaque envelopes. The envelopes were opened after the induction of anesthesia. Patients were divided into two groups. In one group, fentanyl was administered at 8 µg/kg at the beginning of surgery (early-bolus group, *n*=35). In the second group, fentanyl was administered at 6 µg/kg at 60 min before the anticipated end of surgery (late-bolus group, *n*=35). The bolus was injected with two or three pauses to monitor for changes in heart rate. Bradycardia was treated with an intravenous bolus dose of atropine. After fentanyl bolus administration, fentanyl was given continuously at a rate of 0.5 µg/kg/h for postoperative analgesia.

We determined the dose of fentanyl for bolus administration using the TivaTrainer program (Eurosiva.com) for pharmacokinetic simulation to avoid respiratory depression. Since fentanyl produces an analgesic effect at an effect-site concentrations over 1.0 ng/ml and can cause respiratory depression at an effect-site concentrations over 2.0 ng/ml⁷⁾, we targeted an effect-site concentration of 1.5 ng/ml of fentanyl in patients awakening from anesthesia under continuous infusion of fentanyl. The bolus dose of fentanyl was determined to be 6 µg/kg at 60 min before the anticipated end of surgery in the late-bolus group and 8 µg/kg at the beginning of surgery lasting 90 min (the shortest in this study) in the

early-bolus group.

Inhalation of sevoflurane and the infusion of remifentanyl were discontinued at the last staple or suture (T₀). Only verbal stimulation was allowed during this period. The trachea was extubated when end-tidal CO₂ was ≤ 50 mmHg and the respiratory rate was ≥ 12 breaths/min. Recovery from anesthesia was evaluated as the time from T₀ (discontinuation of sevoflurane) until response to verbal commands and the time from T₀ until extubation.

After surgery, patients were transferred to the post-anesthesia care unit (PACU). In the PACU, patients breathed 100% oxygen at a flow rate of 6 L/min. Heart rate, NIBP, SpO₂, respiratory rate, Prince Henry pain score (0 = no pain while coughing, 1 = pain while coughing but not during deep breathing, 2 = pain during deep breathing but not at rest, 3 = slight pain at rest, 4 = severe pain at rest)⁸⁾, sedation grade (0 = awake, 1 = drowsy, 2 = asleep but could be awakened, 3 = deep sleep, difficult to wake up)⁹⁾, incidence of postoperative nausea and vomiting (PONV), and incidence of postanesthetic shivering were evaluated at 0, 5, 10, 15, and 30 min after entering the PACU. Fentanyl 50 µg was administered every time the Prince Henry pain score was 4, and the dose of fentanyl required in the PACU was evaluated. Discharge from the PACU was at the discretion of the attending anesthesiologist when postoperative pain was adequately controlled and postanesthetic shivering had improved. In the ward, the incidence of PONV 24 h after the end of anesthesia was evaluated.

Data analysis

Age, weight, time from T₀ until response to verbal commands, and time from T₀ until extubation were compared between the groups using the Mann-Whitney U test. ASA status and side effects were compared using the χ^2 test. Pain

Table 1 Patient characteristics and duration of surgery and anesthesia

	early-bolus group (n=35)	late-bolus group (n=35)
Age (years)	44.1 ± 6.5	43.2 ± 8.2
Weight (kg)	57.0 ± 8.2	54.6 ± 7.7
ASA physical status (I/II)	16 / 19	17 / 18
Duration of surgery (min)	122 ± 32	119 ± 21
Duration of anesthesia (min)	162 ± 33	164 ± 23

There were no significant differences between the groups. Values are expressed as mean ± SD or *n*.

and sedation scores were analyzed by two-way ANOVA with Turkey–Kramer post hoc analysis. The doses of remifentanyl, ephedrine, and atropine administered during the operation and the dose of fentanyl administered in the PACU were analyzed by one-way ANOVA. The statistical significance level was defined as a *P*-value of <0.05. Data were expressed as mean ± SD.

RESULTS

There were no significant differences between the groups in patient characteristics and duration of surgery or anesthesia (Table 1).

Recovery from anesthesia

Mean time from T₀ until response to verbal commands was 6.7 min in the early-bolus group and 8.1 min in the late-bolus group (*p*<0.05, Table 2). Mean time from T₀ until extubation was 9.0 min in the early-bolus group and 10.3 min in the late-bolus group (*p*<0.05, Table 2).

Table 2 Recovery from anesthesia and administered dose of perioperative drugs

	early-bolus group (n=35)	late-bolus group (n=35)
Time from T ₀ until response to verbal commands (min)	6.7 ± 1.1	8.1 ± 0.9*
Time from T ₀ until extubation (min)	9.0 ± 1.2	10.3 ± 1.1*
Intraoperative		
Remifentanyl (mg)	1.6 ± 0.7	2.0 ± 0.6*
Ephedrine (mg)	7.5 ± 7.5	7.3 ± 6.1
Atropine (mg)	0.29 ± 0.2	0.34 ± 0.3
In the PACU		
Total fentanyl (μg)	77 ± 51	47 ± 41*
Fentanyl administered within 5 min after entering the PACU (μg)	31 ± 78	16 ± 26*

Asterisks indicate statistically significant differences between the groups.

Values are expressed as mean ± SD.

T₀ = discontinuation of sevoflurane

The mean dose of remifentanyl administered during the operation was 1.6 mg in the early-bolus group and 2.0 mg in the late-bolus group (*p*<0.05, Table 2). There were no significant differences between the groups in the dose of ephedrine and atropine administered during the operation (Table 2).

Postoperative pain and pain management

Pain score was significantly lower in the late-bolus group compared with the early-bolus group in the PACU (*p*<0.05, Fig.1). Mean pain score on arrival at the PACU was 2.8 in the early-bolus group and 2.2 in the late-bolus group (*p*<

Fig.1 Prince Henry Pain Score (PHPS) in the two groups during the stay in the PACU.

Values are expressed as mean $\pm$ SD. Asterisk indicates statistically significant differences between the groups ($p < 0.05$).

0.05, Fig.1). Differences in the pain scores between the groups gradually narrowed thereafter (Fig.1). The mean dose of fentanyl administered in the PACU was 77 μ g in the early-bolus group and 47 μ g in the late-bolus group ($p < 0.05$, Table 2). The mean dose of fentanyl administered within 5 min after arrival in the PACU was 31 μ g in the early-bolus group and 16 μ g in the late-bolus group ($p < 0.05$, Table 2).

Hemodynamic responses and incidence of adverse effects

Hypoxemia did not occur in any of the patients in the PACU, nor were there any significant differences in heart rate and NIBP during the PACU stay. Mean respiratory rate at 10 min after arrival in the PACU was 13.4 breaths/min in the early-bolus group and 16.2 breaths/min in the late-bolus group ($p < 0.05$, Fig.2). Mean

Table 3 Incidence of adverse effects

	early-bolus group (n=35)	late-bolus group (n=35)
PONV in the PACU	9 (25)	7 (20)
in the ward	13 (37)	5 (14)*
Postanesthetic shivering	9 (25)	14 (40)

Asterisks indicate statistically significant differences between the groups.

Values are expressed as n (%)

respiratory rates at all other time points in the PACU were similar between the groups. No patient had a respiratory rate below 8 breaths/min at any time in the PACU. The sedation grade also did not significantly differ between the groups (Fig.3). No patient with a sedation grade

Fig.2 Respiratory rate in the two groups during the stay in the PACU.

Values are expressed as mean $\pm$ SD. Asterisk indicates statistically significant differences between the groups ($p < 0.05$).

of 3 or 4 arrived at the PACU, nor was any patient sent to the ward.

The incidence of PONV in the PACU was 25% in the early-bolus group and 20% in the late-bolus group (not significant, Table 3). The incidence of PONV 24 h after the end of anesthesia was 37% in the early-bolus group and 14% in the late-bolus group ($p < 0.05$, Table 3). The incidence of postanesthetic shivering was 25% in the early-bolus group and 40% in the late-bolus group (not significant, Table 3). No patients experienced hypoxia or other adverse events associated with postanesthetic shivering during their stay in the PACU.

DISCUSSION

In the present study, patients administered

6 $\mu\text{g/kg}$ fentanyl at 60 min before the anticipated end of surgery demonstrated improved immediate postoperative pain relief in comparison to patients administered 8 $\mu\text{g/kg}$ fentanyl at the start of surgery. However, the late-bolus group required a longer recovery time from anesthesia compared with the early-bolus group. Sedation grade, incidence of PONV, and incidence of postanesthetic shivering were similar between the groups in the PACU.

Although recovery from anesthesia was significantly delayed in the late-bolus group compared with the early-bolus group in our study, the delay did not affect clinical recovery. Kochs *et al.* compared recovery times after administration of fentanyl with those after morphine given 25 min before the end of major abdominal surgery under remifentanyl–isoflurane anesthesia¹⁰. Median time for extubation was 10.0 min in the fentanyl group, and 9.0 min in the morphine group (no significant difference). They sug-

Fig.3 Sedation grade in the two groups during the stay in the PACU.

Values are expressed as mean $\pm$ SD. There were no significant differences between the groups.

gested that late intraoperative administration of fentanyl or morphine did not markedly affect postoperative recovery. In our study, median time for extubation was 10.3 min in the late-bolus group, similar to that reported by Kochs et al.

No studies have investigated postoperative analgesia after remifentanyl-based anesthesia including timing or dose of fentanyl bolus administration. Munoz et al. analyzed the effect of timing of morphine administration during remifentanyl-based anesthesia ⁹⁾. Compared to intraoperative morphine, fewer reports are available concerning intraoperative fentanyl. Fentanyl has a rapid onset and a smooth transition from intraoperative to postoperative analgesia, with no interruption of early ambulation. Fentanyl also has a long context-sensitive half-time. Derrode et al. compared intraoperative sufentanil with intraoperative remifentanyl for postoperative analgesia after major abdominal

surgery ¹¹⁾. They demonstrated that intraoperative sufentanil had a significant advantage in postoperative analgesia for the pharmacokinetic characteristic of long context-sensitive half-time. Fentanyl has a longer context-sensitive half-time than sufentanil ⁵⁾. Effect-site concentration of fentanyl gradually decreases after the infusion is stopped, which makes it optimal for postoperative analgesia.

In the PACU, there were no significant differences in heart rate or NIBP. Respiratory rate was significantly lower in the early-bolus group compared with the late-bolus group at 10 min after arrival at the PACU. We consider that this is because a significantly higher amount of analgesic was administered to the early-bolus group within 5 min after arrival in the PACU as compared to the late-bolus group. In addition, significantly larger fentanyl doses were administered in the early-bolus group than in the late-bolus group during the PACU stay.

There was no significant difference between the groups in the incidence of PONV during the PACU stay in our study, although PONV occurred slightly more frequently in the early-bolus group than in the late-bolus group. In the ward (24 h after the end of anesthesia), PONV occurred significantly more frequently in the early-bolus group than in the late-bolus group. We consider that this observation is related to the larger dose of fentanyl administered in the early-bolus group during the PACU stay. Camu *et al.* compared the postoperative analgesic and adverse effects of three demand doses of fentanyl (20, 40, and 60 μg) administered by patient-controlled analgesia¹²⁾. Patients who received 20- μg demand dose had significantly higher pain scores than patients who received 60- μg demand dose. Moreover, patients who received 20- μg demand dose consumed the largest dose of fentanyl during the first 24 h postoperatively. Further, PONV occurred more frequently in patients who received 20- μg demand dose compared with patients who received 60- μg demand dose. There was no statistically significant difference between the groups in the incidence of postanesthetic shivering in our study, although it occurred more frequently in the early-bolus group than in the late-bolus group. In our study, significantly higher amounts of remifentanyl were administered intraoperatively in the late-bolus group compared with the early-bolus group. Nakasuji *et al.* reported that high doses of remifentanyl increased the incidence of postanesthetic shivering, and they considered that their result reflected acute opioid tolerance¹³⁾. It is well documented that administration of high doses of opioids may induce acute opioid tolerance, which occur more frequently with short-acting drugs such as remifentanyl¹⁴⁾. Furthermore, Alfonsi *et al.* reported that administration of fentanyl inhibited post-

anesthetic shivering in the PACU¹⁵⁾. Thus, both the higher amounts of fentanyl administered to early-bolus group patients in the PACU and the higher amounts of remifentanyl administered to the late-bolus group patients during the operation may have affected the incidence of postanesthetic shivering in our study.

In conclusion, 6 $\mu\text{g}/\text{kg}$ fentanyl administered at 60 min before the anticipated end of surgery during remifentanyl-based anesthesia provided superior postoperative analgesia in the immediate postoperative period compared with 8 $\mu\text{g}/\text{kg}$ fentanyl administered at the beginning of surgery. Moreover, 6 $\mu\text{g}/\text{kg}$ fentanyl administered at 60 min before the anticipated end of surgery did not markedly affect postoperative recovery.

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