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Efficacy of Intravenous Patient-Controlled Analgesia (IV-PCA) using Fentanyl Compared with IV-PCA Using Morphine after Abdominal Surgery: A Prospective Randomized Study

Yukitoshi Niiyama*, Nobuyoshi Matsuoka, Reona Sugimoto and Michiaki Yamakage

Department of Anesthesiology, Sapporo Medical University School of Medicine, Hokkaido, Japan

***Corresponding author:** Yukitoshi Niiyama, Department of Anesthesiology, Sapporo Medical University School of Medicine, South 1 West 16 Chuo-ku, Sapporo, Hokkaido 060-8556, Japan, Tel: +81-11-611-2111 ext: 3568; Fax: +81-11-631-9683; E-mail: niiyama@sapmed.ac.jp

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Abstract

Objective: To assess the efficacy and adverse effects of fentanyl intravenous (IV) patient-controlled analgesia (PCA) compared with morphine IV-PCA in patients after major abdominal surgery.

Methods: In a prospective, randomized, observer-blinded study, 40 patients with ASA physical status I-II who were scheduled to undergo major abdominal surgery.

A standard general anesthetic was administered. Patients were randomly divided into two groups for 24h postoperatively: 1) Group F with fentanyl concentration of 25 μg/mL, background infusion of 25 μg/h, bolus of 25 μg, and lockout time of 10 min; and 2) Group M with morphine concentration of 1 μg/ml, no background infusion, bolus of 1 mg, and lockout time of 10 min. Numerical rating scale (NRS) pain scores at rest and on coughing and dose of additional PCA bolus and supplemental analgesic, and the incidence of adverse effects were assessed postoperatively during the first 24 h postoperatively.

Results: Compared to Group M, Group F showed significantly lower postoperative pain scores at rest throughout the observation period and on coughing at 2 h after the end of surgery. Incidence of nausea and median dose of antiemetic drugs were comparable between groups. No respiratory complications were encountered in this study. Patient satisfaction scores were significantly higher in Group F than in Group M.

Conclusions: Fentanyl IV-PCA provides more effective postoperative pain relief than morphine IV-PCA and greater patient satisfaction after abdominal surgery, without increasing the incidence of adverse effects.

Keywords: Fentanyl; Morphine; IV-PCA; Postoperative pain; Abdominal surgery; Adverse effects; Patient satisfaction

Introduction

Patient-controlled analgesia (PCA) is a delivery system that allows the patient to self-administer predetermined small doses of analgesic medication for pain relief [1]. Intravenous (IV)-PCA using opioids has been widely adopted for postoperative pain management. Morphine is commonly used for IV-PCA due to its strong analgesic effects, low cost, and evidence of efficacy [2,3]. However, Harrison et al. suggested that an agent with more rapid onset of action and fewer adverse effects might be preferable for IV-PCA [4].

Fentanyl is a mu opioid receptor agonist with several advantageous pharmacological characteristics, including strong analgesic effects (approximately six-times more potent than those of morphine), more rapid onset of action compared to morphine, and a low frequency of adverse effects such as postoperative nausea and vomiting (PONV) or itching [5]. Fentanyl is thus often used for IV-PCA for postoperative pain management. However, little information has been reported regarding the analgesic and adverse effects of fentanyl IV-PCA. The present study was therefore designed to prospectively compare the postoperative analgesia and adverse effects of IV-PCA using fentanyl and morphine in patients undergoing major abdominal surgery.

Methods

After obtaining approval from the institutional review board of the Ethical Committee of Sapporo Medical University Hospitals, Sapporo, Japan and written informed consent from each patient, 40 patients (American Society of Anesthesiologists physical status I-II) scheduled for elective major abdominal laparotomy under general anesthesia were enrolled in this study. Patients were excluded if they were younger than 18 years or older than 80 years of age, weighed less than 40 kg or more than 100 kg, had a history of allergy to opioids, had daily intake of opioids for a period of more than 1 week, had known or suspected drug abuse, were pregnant, or were unable to understand a pain scale or use a PCA device. In this study, patients were blinded to group assignment, which was undertaken using a sealed envelope technique (Group F, n=20; Group M, n=20).

Patients were not premedicated before arriving at the operating room. In the operating room, they were monitored using electrocardiography (ECG), noninvasive and invasive arterial blood pressure, oxygen saturation and end-tidal carbon dioxide concentration. General anesthesia was induced with 1.5-2 mg/kg of IV

propofol. After muscle relaxation had been achieved by IV administration of 0.6 mg/kg rocuronium bromide, the trachea was intubated and controlled ventilation was started. Anesthesia was maintained with remifentanil infused at a rate of 0.1-0.2 μg/kg/min and a mixture of air and sevoflurane (end-tidal concentration, 1-1.5%) in oxygen (40% inspired concentration).

The PCA device used a mechanical pump (CADD Legacy PCA, model 6300; Smiths Medical International, Kent, UK). In Group F, the PCA device was programmed with the following settings: background infusion, 1 mL/h; bolus, 1 mL; lockout time, 10 min; and maximum dose, 6 mL/h, Infusion solutions containing 2.5 mg of fentanyl and 2.5 mg of droperidol were adjusted to 100 mL by dilution with saline (concentration of fentanyl, 25 μg/mL). In Group M, the PCA device was programmed with the following settings: no background infusion; bolus, 1 mL; lockout time, 10 min; and maximum dose, 6 mL/h. Infusion solutions containing 100 mg of morphine combined with 2.5 mg of droperidol were adjusted to 100 mL by dilution with saline (concentration of morphine, 1 mg/mL). When closing the peritoneum, all patients received IV administration of titrated doses of 0.6 mg/kg of fentanyl in Group F and 0.15 mg/kg of morphine in Group M, and IV-PCA treatment was started. At the end of surgery, all patients received 1.25 mg of droperidol and 50 mg of flurbiprofen intravenously. Intensities of postoperative pain at rest and on coughing were evaluated using a numerical rating scale (NRS), from 0 ("no pain") to 10 ("worst pain imaginable"). After extubation, adequate analgesia was defined as NRS <2 at rest. Patients were intravenously administrated 100 μg of fentanyl or 1 mg of morphine every 10 min when they experienced pain at rest. If adequate analgesia was obtained (NRS <2), patients were taken from the operation room. When analgesia was considered inadequate by the patient, an additional PCA bolus was given. If the patient had not obtained pain relief despite additional bolus doses, 50 mg of IV flurbiprofen was administered as a supplemental analgesic on patient request. The Observer Assessment of Alertness/Sedation Scale (OAA/S) was used to determine the level of sedation [6] (Table 1).

For patients experiencing nausea, with or without vomiting, 10 mg of metoclopramide was given intravenously. Oxygen (2 L/min) was administration for 24 hours postoperatively in all cases. During the first 24 h postoperatively, non-invasive artery blood pressure, heart rate, oxygen saturation, respiratory rate and occurrence of untoward events were recorded at 2h intervals. Hypotension (30% reduction in systolic blood pressure compared with preoperative baseline) was treated using a vasopressor and/or IV fluid at the investigator's discretion. If a respiratory rate of less than 8 breaths/min for a period longer than 20 min was observed, the PCA pump was stopped. NRS at rest and on coughing, the incidence of nausea, and OAA/S scale were recorded at 2, 6, 12, and 24 h after the end of surgery. The degree of patient satisfaction was evaluated using a NRS, from 0 ("dissatisfaction") to 10 ("satisfaction") at 24 h after the end of surgery.

On the basis of preliminary data, power analysis was performed using postoperative pain on coughing as the primary outcome variable. We aimed to achieve a between-group mean difference in NRS of 1.5 when comparing the reduction in pain scores in the fentanyl group to those in the morphine group, with a type 1 error rate of one-tailed $\alpha=0.05$, and the alternate hypothesis that the null hypothesis would be retained with a type error of $\beta=0.2$. Our analysis indicated that this would require groups of 12 patients. NRS data are presented as medians (25th-75th percentiles) and other data are presented as means ± standard deviations.

The chi-square test was used to analyze demographic data and numbers of patients receiving supplemental analgesia and reporting nausea and itching. The Wilcoxon-Mann-Whitney test followed by Scheffe's test were used to analyze NRS, consumption of flurbiprofen and metoclopramide, respiratory rate, and OAA/S scale. Values of $p<0.05$ were considered statistically significant.

Responsiveness	Speech	Facial expression	Eye	Score
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation	Glazed and marked ptosis	3
Responds only after mild prodding or shaking	Few recognizable words	-	-	2
Does not respond to mild prodding or shaking	-	-	-	1

Table 1: Observer assessment of alertness/sedation (OAA/S) scale.

Results

One patient in Group M was excluded because of severe nausea and vomiting. No significant differences were observed between the remaining 39 patients in terms of age, sex ratio, height, weight or surgical procedures between groups (Table 2).

Postoperative pain scores at rest and on coughing are presented in Figure 1. NRS scores at rest were significantly lower in Group F than in Group M throughout the observation period. NRS scores on coughing were significantly lower in Group F than in Group M only at 2 h after the end of surgery.

Although the number of patients receiving PCA bolus doses and the number of additional PCA bolus doses were similar between groups, numbers of patients receiving supplemental analgesic were significantly smaller in Group F (4/20) than in Group M (15/19; $p<0.01$), and the median number of doses of supplemental analgesic was larger in Group M than in Group F ($p<0.01$) (Table 3).

Incidence of nausea and median dose of antiemetic drug were comparable between groups (Table 4). Two patients in Group F showed a score of 4 on the OAA/S scale on the day of surgery. Three patients in Group M had a score 4 on the scale at 2 and 4 h after surgery, but showed scores of 5 on the OAA/S scale at 12 h after the end of surgery.

The remaining patients in the two groups showed scores of 5 on the OAA/S scale on the day of surgery. No significant differences were apparent between groups. Respiratory depression as indicated by a decrease in respiratory rate less than 8 breaths/min was not observed in any patient during the study. Oxygen saturation was maintained at more than 92% in all cases. No hypotension was observed in either group. NRS scores for patient satisfaction were significantly higher in Group F than in Group M ($p<0.05$) (Figure 2).

Patient characteristics	Group F	Group M
No. of patients	20	19
Sex (M/F)	10/10	9/10
Age (years)	54.3 ± 15.0	54.7 ± 17.2
Weight (kg)	59.7 ± 16.1	59.0 ± 10.7
Height (cm)	57.3 ± 15.0	57.3 ± 15.0
Surgical Procedures		
Upper abdominal surgery	7	6
Total or distal gastrectomy	2	2
Splenectomy	2	3
Others	3	1
Lower abdominal surgery	13	13
Bowel resection	3	4
Nephrectomy	6	5
Graft replacement for abdominal aortic aneurysm	1	1
Abdominal total hysterectomy	3	2
Others	1	1

Table 2: Patient characteristics and surgical procedures. Data are presented as mean ± SD or number of patients. No significant difference between groups.

	Group F	Group M
Number of the patients receiving additional PCA bolus doses	18	19
Number of doses of PCA bolus	14.5 (0-44)	17.0 (0-27)
Number of the patients receiving a supplemental analgesic	4*	15
Number of doses of supplemental analgesic	0 (0-2)*	2 (0-4)

Table 3: Dose of additional PCA bolus and supplemental analgesic. Data are presented as number of patients or median (range); *p<0.05 vs. Group M.

	Group F	Group M
Number of the patients with nausea	7	6
Number of doses of antiemetic agents	0 (0-2)	0 (0-4)

Table 4: Incidence of PONV and doses of antiemetic agents. Data are presented as number of patients or median (range). No significant difference between groups.

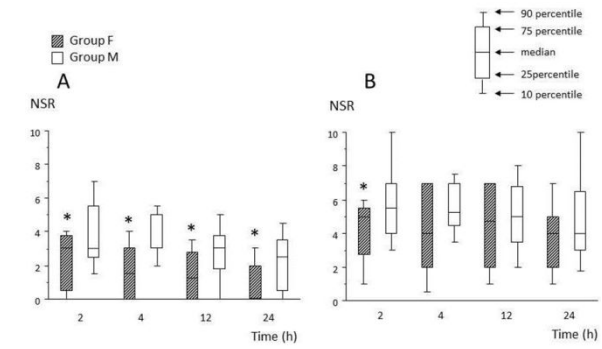

Figure 1: Numerical Rate Scale (NRS) at rest (A) and on coughing (B). Data are presented as median (25^{th}-75^{th} percentile). Group F, group fentanyl; Group M, group morphine. *p<0.05 vs. Group M.

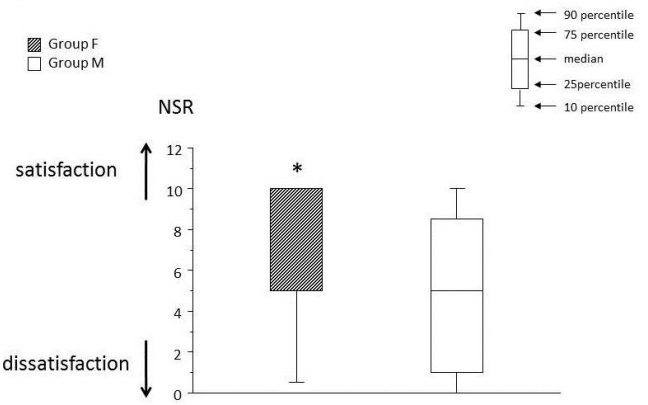

Figure 2: Numerical Rate Scale (NRS) of patients' satisfaction. Data are presented as median (25th-75th percentile). Group F, group fentanyl; Group M, group morphine. *p<0.05 vs. Group M

Discussion

In this study, lower pain scores both at rest and on coughing were observed in patients receiving IV-PCA with fentanyl when compared to patients receiving IV-PCA with morphine after major abdominal surgery, without any apparent increase in the incidence of adverse effects. Furthermore, the number of patients receiving supplemental analgesics was lower in Group F than in Group M. These results indicate that IV-PCA for postoperative analgesia is more effective with fentanyl than with morphine.

The reasons why morphine did not provide superior analgesic effects in this study may be due to the differences pharmacological profiles of these two opioids. First, the onset of analgesic effects is more rapid with fentanyl than with morphine. Since fentanyl shows 160-fold greater liposolubility than morphine, penetration into tissues and elicitation of analgesic effects is much quicker [7]. Analgesic effects of bolus administration can thus be rapidly achieved for patients when they feel pain.

Second, titrated doses of morphine may have been insufficient. In Group M, analgesia, especially that on coughing, appeared inadequate

in the early postoperative period. Providing an adequate level of comfort before starting PCA is central to the success of this approach. In our hospital, not all patients are followed in the recovery room postoperatively. Titration may have been insufficient due to fear of sedation and respiratory depression.

Third, in Group F, stable blood concentrations of fentanyl induced by background infusion may have facilitated reliable analgesia. The minimum effective blood concentration (MEAC) of fentanyl required for analgesia is reportedly 0.6-3 ng/mL [8]. Although we did not investigate blood concentrations of drugs in this study, background infusion of fentanyl may prevent blood concentrations from falling below the MEAC. When morphine is used for IV-PCA, background infusion can increase the incidence of sedation and respiratory depression without reducing the number of demands or the analgesic requirements [9]. Routine use of background infusion is thus not recommended for IV-PCA with morphine. However, the duration of action is shorter for fentanyl than for morphine. Background infusion is thus often needed for protocols using fentanyl IV-PCA. Paul et al. reported that for IV-PCA with fentanyl, a dose protocol using only a bolus dose without background infusion did not provide adequate postoperative pain relief after cesarean section compared with IV-PCA using morphine [10]. Norfentanyl, the metabolite of fentanyl created by CYP3A4, is less potent and shows lower affinity for the mu receptor [11], and can thus be used for patients with renal failure, although CYP3A4 inhibitors or liver dysfunction may lead to increased blood levels of fentanyl. The lipophilic pharmacokinetics of fentanyl also lead to deposition in adipose tissue. Long-term continuous infusion can prolong the context-sensitive half-life. Rather than terminal elimination, it has been proposed that 50% elimination is a more clinically relevant measure of decreasing drug concentration after constant infusion for a given duration [12]. Combined with background infusion, fentanyl is accumulated and may increase the risk of sedation or respiratory dysfunction during opioid infusion. As a result, continuous monitoring of the level of consciousness and respiratory rate needed when background infusion is used.

Despite the fact that fentanyl causes less nausea than morphine, the incidence of nausea and median doses of antiemetic drugs were comparable between groups. This might be attributable to the increased dose of fentanyl administered with background infusion.

One of the reasons why morphine is often used for IV-PCA is that morphine is inexpensive compared with fentanyl. As of the time of writing, hospital costs for providing an average patient with PCA for 24 h is 7.09 US dollars for morphine (mean of 18.69 mg) and 41.71 US dollars for fentanyl (mean of 1,078.25 μg), representing an almost 6-fold difference. The increased cost of PCA fentanyl was not associated with any obvious benefit.

Recently, the Enhanced Recovery after Surgery (ERAS) protocol was developed to enhance postoperative recovery. The aims of ERAS are to decrease surgical stress response, accelerate recovery, decrease complication and mortality rates, minimize the duration of hospitalization and reduce health costs [13,14]. Most evidence regarding ERAS from prospective studies has related to patients undergoing colorectal surgery. The ERAS protocol recommends continuous thoracic epidural infusion using local anesthetics with or without opioids for managing postoperative pain following colorectal surgery [15]. Opioid-based analgesia does not provide equally efficient analgesia and has fewer beneficial effects on surgical stress responses compared with epidural analgesia, as follows: 1) inadequate analgesic effects, especially when moving; 2) increased PONV; 3) delayed recovery of bowel function; and 4) sedation or respiratory depression. However, some patients are contraindicated for epidural analgesia, such as anti-coagulated patients, patients with systemic sepsis, patients with neuronal disorders, and patients in whom epidural catheterization is technically impossible. In the ERAS protocol, what kind of postoperative management should be carried out is not explained. IV-PCA with an opioid plays a crucial role because of its strong analgesic effect and evidence-based efficacy. IV-PCA with fentanyl can be one factor in multimodal analgesia for managing postoperative pain. However, effective analgesia is associated with variable degrees of nausea, sedation, and respiratory depression. It is recommended that postoperative management be carried out using a multimodal approach to decrease doses of opioid combined with non-steroidal anti-inflammatory drugs, acetaminophen, peripheral neural block, and infusion of local anesthetics.

In summary, the present results indicate that IV-PCA is more effective with fentanyl than with morphine for relieving postoperative pain following major abdominal surgery and has higher patient satisfaction, without causing any appreciable increase in the incidence of nausea or hypotension. However, continuous monitoring of the level of consciousness and respiratory rate is needed due to the risk of sedation or respiratory dysfunction when background infusion is being used.

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