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Comparison of the Analgesic Effect of Patient-controlled Oxycodone and Fentanyl for Pain Management in Patients Undergoing Colorectal Surgery

Authors

Kyeo-Woon Jung (1), Hyeon-Wook Kang (2), Chan-Hye Park (1), Byung-Hyun Choi (3), Ji-Yeon Bang (1), Soo-Han Lee (4), Eun-Kyung Lee (5), Byung-Moon Choi (1), Gyu-Jeong Noh (1,6)

(1) Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

(2) University of Ulsan College of Medicine, Seoul, Korea

(3) Department of Surgery, Pusan National University Yangsan Hospital, Yangsan, Korea

(4) Division of Drug Safety Evaluation New Drug Development Center, Osong Medical Innovation Foundation, Chungju-si, Chungbuk, Korea

(5) Department of Statistics, Ewha Womans University, Seoul, Korea

(6) Department of Clinical Pharmacology and Therapeutics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Corresponding author

Byung-Moon Choi, M.D., Ph.D.: Assistant Professor, Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Mailing address: 388-1, Pungnap 2-dong, Songpa-gu, Seoul 138-736, Korea

Tel: +82-2-3010-1704

Fax: +82-2-3010-6790

E-mail: byungmoonchoi7@gmail.com

Kyeo-Woon Jung and Hyeon-Wook Kang contributed equally to this work as first authors.

Running title

Analgesic effects of patient-controlled oxycodone

Key words

Fentanyl, Oxycodone, Pain relief

Abstract

Oxycodone is a μ-opioid receptor agonist and is generally indicated for the relief of moderate to severe pain. The aim of this study was to compare the analgesic efficacy of patient-controlled oxycodone and fentanyl for postoperative pain in patients undergoing colorectal surgery. Patients scheduled to undergo elective colorectal surgery (n=82) were allocated to receive oxycodone (n=41, concentration of 1 $mg \cdot ml^{-1}$) or fentanyl (n=41, concentration of 15

μg·ml^{-1}) for postoperative pain management. After the operation, pain using a numerical rating scale (NRS), delivery to demand ratio, infused dose of patient-controlled analgesia (PCA), side effects, and sedation levels were evaluated. Median (25–75%) cumulative PCA dose of oxycodone group at 48 h (66.9, 58.4–83.7 ml) was significantly less than that of fentanyl group (80.0, 63.4–103.3 ml, *P*=0.037). Six hours after surgery, the mean (SD) NRS scores of the oxycodone and fentanyl groups were 6.2 (2.4) and 6.8 (1.9), respectively (*P*=0.216). The mean equianalgesic potency ratio of oxycodone to fentanyl was 55:1. The groups did not differ in postoperative nausea, vomiting, and level of sedation. Patient-controlled oxycodone provide similar effects for pain relief compared to patient-controlled fentanyl in spite of less cumulative PCA dose. Based on these results, oxycodone can be a useful alternative to fentanyl for PCA in patients after colorectal surgery.

Introduction

Oxycodone is a μ-opioid receptor agonist and is generally indicated for the relief of moderate to severe pain.[1,2] In recent years, the use of intravenous oxycodone has increased markedly. As a result, it has replaced morphine as the first-line choice of opioid in several countries.[2] In Korea, intravenous oxycodone was approved for postoperative intravenous patient-controlled analgesia (PCA) by the Ministry of Food and Drug Safety (MFDS) in 2013. The dosage regimen for postoperative pain relief with intravenous oxycodone that was approved by MFDS is an intravenous bolus loading of 2 mg followed by PCA composed of demand boluses of 1 mg and no background infusion with an oxycodone concentration of 1 mg/ml. Although clinical experiences of postoperative pain management with oxycodone have been reported in Europe,[3,4] fentanyl is the most commonly used opioid for PCA-based postoperative pain management in Korea. Whether oxycodone can be an alternative to fentanyl remains unclear. In particular, to the best of our knowledge, the analgesic efficacies

of patient-controlled oxycodone and fentanyl after major abdominal surgery have not been compared directly. Also, the potency ratio of oxycodone to fentanyl has not yet been fully evaluated. In a previous study, analgesic efficacy of intravenous oxycodone and fentanyl were compared at postanesthesia care unit (PACU) in patients undergoing laparoscopic cholecystectomy.[5] The median consumption of oxycodone and fentanyl was 15 mg and 200 μg, respectively, and the intensity of abdominal pain was significantly lower in the oxycodone group, indicating that the potency ratio of oxycodone to fentanyl was less than 75:1.[2,5] In a recent pilot study, the potency ratio was 60:1 in patients undergoing laparoscopic gynecologic surgery.[6]

Therefore, the aim of this study was to compare the analgesic effects of patient-controlled oxycodone and fentanyl for postoperative pain management in patients undergoing colorectal surgery. In addition, the potency ratio of oxycodone to fentanyl was explored using the log data of the electronic PCA pump.

Results

In total, 82 patients (n=41 in each group) were enrolled in the study. Since there were no drop-outs, all patients were included in the analyses. The characteristics of the fentanyl and oxycodone PCA patient groups are summarized in Table 1. In Korea, all regular employees should visit a medical center for a yearly medical checkup by labor lows and, hence, the overall prevalence of colorectal cancer screening was high. This policy has enabled ASA I or II patents to be enrolled in this study. The two groups did not differ significantly in terms of age, weight, height, gender, or type of surgery. In a previous study, lean body mass and age were significant covariates for the volume of distribution and metabolic clearance in the final pharmacokinetic model of oxycodone, respectively.[7] Patients with similar demographic characteristics between the two groups were enrolled to minimize pharmacokinetic

variability. The numerical rating scale (NRS) for pain and the delivery to demand ratio over time after the end of surgery is shown in Figure 1 and 2, respectively. The two groups did not differ in terms of NRS for pain and delivery to demand ratio at any of the time points, irrespective of type of surgery. Visual inspection of Figure 1 shows that NRS for pain tended to decrease over time. Consistent with this, the delivery to demand ratio tended to increase over time.

The cumulative volumes of PCA that were consumed 6–120 h after the end of surgery are depicted in Table 2. The oxycodone group had significantly smaller cumulative volumes at all six time points than the fentanyl group (Mann-Whitney U test, $P<0.05$). Median (25–75%) cumulative PCA dose of oxycodone group at 48 h (66.9, 58.4–83.7 ml) was significantly less than that of fentanyl group (80.0, 63.4–103.3 ml, $P=0.037$). The cumulative amount of PCA was calculated by multiplying the cumulative volume with the opioid concentration.

The number of patients receiving rescue analgesics, frequency and the total amount of rescue analgesics administered are presented in Table 3. The oxycodone and fentanyl groups did not show statistically significant differences. Almost all the patients required rescue analgesics at postanesthesia care unit and about 50% patients received tramadol or pethidine to achieve lower pain scores on the day of operation. Since Figures 1, 2 and Table 3 suggest that patient-controlled oxycodone and fentanyl had comparable analgesic effects in terms of postoperative pain management, the cumulative amount of PCA can be used to indicate potency ratio of oxycodone to fentanyl. The mean (95% confidence intervals) equianalgesic potency ratio of oxycodone to fentanyl was 55:1 (54:1–57:1).

The median (25–75%) elapsed time before first passage of flatus was 79.8 (65.8–94.2) h for the oxycodone group and 73.9 (67.5–101.1) h for the fentanyl group (Mann-Whitney U test, $P=0.681$). Postoperative nausea and vomiting (PONV) and sedation levels of the patients were assessed based on the Rhodes index of nausea vomiting retching (RINVR) and the

Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale, respectively. The patients in both groups showed similar incidence of PONV and sedation levels (Table 4).

Discussion

When the analgesic effects of two patient-controlled opioids are compared, it is important to determine the PCA dosage regimens of the two opioids because they affect the efficacy of the analgesia. Previous studies have shown that the potency ratio of oxycodone to morphine is 1:1, whereas the potency ratio of morphine to fentanyl is 100:.1.[4,8] Two studies comparing patient-controlled oxycodone and fentanyl in patients who underwent laparoscopic cholecystectomy and hysterectomy showed that the cumulative oxycodone dose was lower than the cumulative fentanyl dose.[9,10] Moreover, a study comparing patient-controlled oxycodone and fentanyl in patients undergoing laparoscopic hysterectomy or myomectomy showed that, when the potency ratio of oxycodone to fentanyl was 60:1, the two opioids had similar analgesic effects.[6] We found that the mean equianalgesic potency ratio of oxycodone to fentanyl was 55:1. This potency ratio is similar to the oxycodone to fentanyl potency ratios reported previously in two studies on other populations.[5,6] Thus, Koch *et al.* showed that in patients who underwent laparoscopic cholecystectomy, intermittent administration of intravenous oxycodone up to 15 mg yielded better analgesia than fentanyl 200 μg, which indicates that the potency ratio of oxycodone to fentanyl was less than 75:1.[2,5] Similarly, the pilot study of Park *et al.* showed that oxycodone was more effective than fentanyl after laparoscopic gynecological surgery at a ratio of 100:1 and that the two analgesics were equipotent at 60:1.[6] However, the sample sizes of these studies and our own were relatively small, which may limit their reliability. Studies testing various potency ratios in a large cohort are needed to determine the appropriate potency ratio of oxycodone to fentanyl.

In this study, the cumulative oxycodone consumption during the first 48 postoperative hours (CUM_{48h}) was less than those of other previous studies to evaluate the efficacy of patient-controlled oxycodone in patients undergoing coronary artery bypass study.[11,12] This difference may be explained by the difference of type of surgery. Actually, the CUM_{48h} in patients undergoing laparoscopic cholecystectomy was about half of this study.[9] Another cause can be a difference of demand bolus dose. In previous studies, the demand bolus dose of PCA device was twice the amount administered in this study.[11,12]

NRS for pain is a relatively subjective parameter to evaluate the severity of pain and delivery to demand ratio is an objective parameter. As presented in Figure 2, delivery to demand ratio slightly increased over time, indicating that postoperative pain slightly subsided. The lockout time is the interval after a successful demand during which the PCA device is refractory to further demands by the patient. This interval is a necessary safeguard to minimize the risks of opioid-induced side effects. Delivery to demand ratio at 6 h after the end of surgery was about 60%, indicating that patients pushed the PCA button about 40% of all request during the lockout time. This means that patients did not receive adequate relief of postoperative pain. It is necessary to improve dosing strategy of postoperative pain management in patients undergoing colorectal surgery.

There were several issues to be considered as limitations of this study. First, the amount of rescue analgesics was not considered when calculating the potency ratio of oxycodone to fentanyl, which could lead to drawing improper conclusion. However, there were no statistically significant differences in frequency and the amount of rescue analgesics between the two groups (See Table 3). Therefore, rescue analgesics might not be considered as a determinant when calculating the potency ratio. Second, undertreatment of postoperative pain

was observed during the observation period. In Korea, surgeons have conducted postoperative pain management and were inclined to reduce use of opioid because opioids may disturb the recovery of bowel movement. This observational study was designed to compare the analgesic effects of patient-controlled oxycodone and fentanyl, and the only intervention was the determination of PCA dosage regimens of the two opioids. Although this inadequate pain control was a major problem in this study, this limitation has no direct effect on comparison of analgesic effect between two opioids. From now on, active efforts should be made to improve postoperative pain management and these results can provide reference data for acute pain management. Third, this study was not a randomized clinical trial. Patients enrolled in this study between June 2013 and August 2013 received fentanyl PCA and patients enrolled between September 2013 and November 2013 received oxycodone PCA. Because clinical experiences of postoperative pain management with oxycodone were extremely limited in Korea, analgesic effects of oxycodone were evaluated in consecutive patients after the completion of the fentanyl PCA group. However, the adoption of non-randomization is not likely to have affected the results because the gap of time between the trials of the two groups was small and the only intervention was the determination of PCA dosage regimens.

In conclusion, the analgesic effect of patient-controlled oxycodone and fentanyl was similar when the PCA regimens consisted of a demand bolus of 1 mg for oxycodone and 15 μg for fentanyl, a lockout time of 15 min, and background infusion of 1 $mg \cdot h^{-1}$ for oxycodone and 15 $\mu g \cdot h^{-1}$ for fentanyl with an oxycodone concentration of 1 $mg \cdot ml^{-1}$and a fentanyl concentration of 15 $\mu g \cdot ml^{-1}$. The mean equianalgesic potency ratio of oxycodone to fentanyl was 55:1. The two opioids did not differ significantly in terms of the rates of postoperative nausea and vomiting, and level of sedation.

Methods

Patient population

This prospective observational study was conducted between June 2013 and November 2013. The subjects (n=41) in the fentanyl group were enrolled between June and August and the subjects in the oxycodone group (n=41) between September and November. This study was approved by the Asan Medical Center Institutional Review Board (approval number: 2013–0854) and registered on an international clinical trials registry platform (http://cris.nih.go.kr, KCT0001854). Patients who were between 40 and 79 years of age who were scheduled for elective open or laparoscopic colorectal surgery were enrolled if their American Society of Anesthesiologists (ASA) physical status was I or II and they consented to receive intravenous PCA. In a previous study, lean body mass and age were significant covariates for the volume of distribution and metabolic clearance in the final pharmacokinetic model of oxycodone, respectively.[7] Patients with similar demographic characteristics between the two groups were enrolled to minimize pharmacokinetic variability. The exclusion criteria included hypersensitivity to oxycodone or any of the excipients, pregnant or lactating women, where pregnancy is defined as the state of a female from conception, confirmed by a positive urine pregnancy test, until the termination of gestation, severely impaired respiratory function or respiratory depression status, convulsive disorders, head injury, shock, a reduced level of consciousness of uncertain origin, intracranial lesions or increased intracranial pressure, or patients with severe hepatic impairment, concurrent medication of other central nervous system depressants that may cause respiratory depression, hypotension, profound sedation or potential coma, clinically significant impairment of cardiovascular, respiratory or renal function.

Study endpoints

The primary endpoint of this study was to compare the efficacy of patient-controlled oxycodone and fentanyl by measuring the pain with a numerical rating scale (NRS) for pain and by measuring the delivery to demand ratio. The NRS score of pain runs from 0 to 10, where 0 is no pain and 10 is the worst pain imaginable. The delivery to demand ratio was calculated as follows:

$$Delivery\ to\ demand\ ratio\ (\%) = \frac{number\ of\ completed\ deliveries\ to\ the\ patient}{number\ of\ requests\ made\ by\ pushing\ the\ PCA\ button} \times 100$$

A high ratio indicates that the patient's demands were frequently met by delivery of the drug, whereas a low ratio suggests that the patient pushed the PCA button frequently during the lockout interval.[13] The secondary study endpoint was to evaluate the potency ratio of oxycodone potency to fentanyl potency. Finally, the frequency and amount of rescue analgesics that were used and the safety profiles of the two analgesics (including postoperative nausea, vomiting, and sedation) were evaluated. NRS for pain was recorded by nurses who were blinded to the patient's group. Delivery to demand ratio was calculated from the log data of the electronic PCA pump (Accumate 1100; Wooyoung Medical Co. Ltd., Seoul, Korea). Both NRS for pain and delivery to demand ratio were assessed 1, 6, 12, 24, 48, 72, and 120 h after the end of surgery. Postoperative nausea and vomiting were evaluated using the Rhodes index of nausea vomiting retching (RINVR) on postoperative days 1 and 2. RINVR is a reliable and valid instrument that consists of eight 5-point self-report items that are designed to assess subjective and objective factors of nausea, vomiting, and retching in various situations, including in surgical patients.[14] The recovery of bowel function was evaluated by measuring the time between the end of surgery to the first passage of flatus. The Modified Observer's Assessment of Alertness/Sedation (MOAA/S) scale was used to assess the level of sedation on postoperative days 1 and 2.[15]

Investigational drugs

The oxycodone and fentanyl used in this study were10 $mg \cdot ml^{-1}$ OxyNorm® (oxycodone, Mundipharma, Seoul, Korea) and 50 $\mu g \cdot ml^{-1}$ Fentanyl Citrate GuJu INJ (fentanyl citrate, DAI HAN Pharm, Seoul, Korea), respectively.

Simulation study to determine the optimal dosing regimen of patient-controlled oxycodone

The dosing regimen of the patient-controlled oxycodone group partly reflected the approval criteria of the MFDS: the loading dose was 2 mg, the oxycodone concentration was 1 $mg \cdot ml^{-1}$, the demand bolus was 1 mg, no background infusion, and the lockout interval was 15 min. However, we changed the loading dose and background infusion as a result of our pilot simulation study. This simulation study was based on the pharmacokinetic parameters and values of minimum effective concentration (MEC, as indicated by the need to administer intravenous opioid due to pain) and minimum effective analgesic concentration (MEAC, as indicated by relief of pain by administering opioid)for oxycodone that were obtained by previous studies.[7,16,17] Deterministic simulations that did not consider either inter-individual or intra-individual random variability were performed using Asan Pump software (version 2.1.3; Bionet Co. Ltd., Seoul, Korea, http://www.fit4nm.org/download, last accessed: Aug 27, 2012). The simulation study showed that when the oxycodone loading dose was that approved by the MFDS (2 mg), it generated plasma oxycodone concentrations over time after surgery that were below MEC (Figure 3A). By contrast, when 0.1 $mg \cdot kg^{-1}$ oxycodone (6 mg for a 60kg person) was administered as the loading dose, it generated concentrations higher than MEC for 1 h after the end of surgery (Figure 3B). In another simulation, an intravenous oxycodone loading dose of 2 mg or 0.1 $mg \cdot kg^{-1}$ was administered at the end of surgery and intravenous PCA with or without 1 $mg \cdot h^{-1}$ background infusion was started 5 min later. Table 5 summarizes the time to reach MEAC, the time to reach 90% steady state concentration, and

the steady state concentration of oxycodone. During the immediate postoperative period, MEAC was most quickly reached when the higher loading dose (0.1 $mg \cdot ml^{-1}$) and background infusion were used.

We also found that during the immediate postoperative period, MEAC was reached most quickly using both the higher loading dose (0.1 $mg \cdot kg^{-1}$) and background infusion. However, even with this dosage regimen, rescue analgesics were often required to relieve pain for at least 2 h after the end of surgery. These observations resulted in the following oxycodone intravenous PCA regimen. The oxycodone PCA consisted of 1 $mg \cdot ml^{-1}$ oxycodone in a volume of 200 ml, and it started with an intravenous bolus loading of 0.1$mg \cdot kg^{-1}$ and was followed by demand boluses of 1mg with a background infusion of 1$mg \cdot h^{-1}$. The fentanyl PCA regimen consisted of 15 $\mu g \cdot ml^{-1}$ fentanyl in a volume of 200 ml that was administered according to the usual clinical practice guidelines at our institution, namely, intravenous bolus loading of 0.2 $\mu g \cdot kg^{-1}$ followed by demand boluses of 15 μg with 15 $\mu g \cdot h^{-1}$ background infusion. The lockout interval of two PCA regimens were 15 min.

Study procedure

All patients fasted starting at midnight. Once in the operating theatre, the patients were monitored with electrocardiography, pulse oximetry, end-tidal carbon dioxide partial pressure and bispecral index (BIS, Aspect 2000, Aspect Medical Systems, Inc., Newton, MA, USA). Propofol and remifentanil were administered by a target effect-site concentration-controlled infusion (Asan Pump, version 1.3, Bionet Co., Ltd., Seoul, Republic of Korea) using the modified Marsh and Minto models.[18,19] If necessary, ephedrine or atropine was administered during anesthesia to maintain systolic blood pressure (SBP) above 80 mmHg and heart rate (HR) above 45 beats/min. All patients were administered oxycodone 0.1 $mg \cdot kg^{-1}$ or fentanyl

0.2 μg·kg^{-1} 30 min before the end of surgery, after which intravenous PCA infusion was started. At the end of surgery, the neuromuscular block was antagonized by administering glycopyrrolate and neostigmine.

Rescue analgesics

If NRS was more than 4 in the postanesthesia care unit (PACU), patients in the oxycodone group received oxycodone 2 mg, and patients in the fentanyl group received fentanyl 50 μg. These bolus doses were administered at 15-min intervals until NRS was 4 or less. Postoperative pain management in general ward was conducted by general surgeons according to the usual clinical practice at the Department of Surgery (If NRS was more than 4 or 7, patients received tramadol 50 mg or pethidine 25 mg, respectively). All surgeons were blinded to the patient's allocation.

Statistics

A preliminary study to determine the appropriate sample size was conducted by measuring the pain (using the NRS) of 20 patients 12 h after they underwent colorectal surgery and then received patient-controlled oxycodone and fentanyl. This study showed that a sample size of 41 patients per treatment arm would be sufficient to detect a 1.5-point difference in NRS 12 h after the end of surgery with 80% power at an alpha of 0.05. In general, a minimum 30% difference between groups in analgesia using a 0–10 scale was a clinically meaningful difference.[20,21] In the preliminary study, 30% difference at 12 h after the end of surgery was about 1.5-point. This sample size is comparable to the sample sizes used in previous studies.[5,9] All statistical analyses were conducted using R (version 3.2.2, R Foundation for Statistical Computing, Vienna, Austria) or SigmaStat 3.5 for Windows (Systat Software, Inc., Chicago, IL, USA). Normally distributed continuous, non-normally distributed continuous,

and categorical variables were expressed as mean (SD), median (25–75%), and counts and percentages, respectively. *P*-values of 0.05 were considered to be statistically significant.

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Disclosure of Competing Interests

The authors declare that there are no conflicts of interest.

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Table 1. Demographic and clinical characteristics of the patients

	Oxycodone (n=41)	Fentanyl (n=41)
Age, yr	57.8 ± 10.3	57.8 ± 10.4
Weight, kg	61.3 ± 11.4	61.8 ± 8.4
Height, cm	163.2 ± 8.5	162.2 ± 8.9
Sex (M/F)	25/16	22/19
ASA PS I/II	5/36	1/40
Surgical diagnosis		
Colorectal cancer	38	39
GIST	2	1
Others*	1	1
Type of surgery†		
Open colorectal surgery	22	22
Laparoscopic colorectal surgery	19	19
Duration of anesthesia, min	160 (129–177)	152 (118–180)
Total amount of propofol, mg	821.3 (678.3–1000.0)	793.2 (684.1–967.1)
Total amount of remifentanil, mg	3.6 (2.8–4.3)	3.4 (2.8–4.6)

The data are expressed as means±SD or as counts, as appropriate. ASA PS: American Society of Anesthesiologists Physical Status, GIST: gastrointestinal stromal tumor, The patient groups were compared in terms of their characteristics using the two-sample t-test or Chi-squared test, as appropriate. The oxycodone and fentanyl groups did not differ significantly in terms of any of the variables.*: small bowel bleeding and intraabdominal abscess, †:operation name (number of patients, oxycodone/fentanyl): right hemicolectomy (4/3), left hemi colectomy (2/2), anterior resection (4/0), low anterior resection (5/6), ultralow anterior resection (6/4), small bowel resection and anastomosis (1/2), laparoscopic right hemicolectomy (7/10), laparoscopic left hemicolectomy (0/1), laparoscopic ileocecal resection (1/0), laparoscopic anterior resection (2/7), laparoscopic low anterior resection (8/1), laparoscopic small bowel resection and anastomosis (1/0), abdominoperitoneal resection (0/2), appendectomy, incision and drainage (0/1), total pelvic exenteration (0/1), Hartmann's operation (0/1).

Table 2. Cumulative volume (ml) of patient-controlled oxycodone and fentanyl

Elapsed time after the end of operation (h)	Oxycodone (n=41)	Fentanyl (n=41)
6	14.7±5.0	17.6±5.8*
12	21.9 (17.2–29.6)	27.3 (20.1–36.0)*
24	37.3 (33.0–46.1)	46.5 (38.4–61.1)*
48	66.9 (58.4–83.7)	80.0 (63.4–103.3)*
72	93.1 (82.9–115.7)	111.1 (94.9–135.3)*
120	123.8±33.0	144.8±34.2*

The data are expressed as means±SD or median (25−75%), as appropriate. The patient groups were compared in terms of cumulative volume of PCA using Student's t-test or Mann-Whitney Utest, as appropriate. *P<0.05 *vs.* oxycodone.

Table 3. Number (N) of patients receiving rescue analgesics, frequency (F) and total amount (A) of those.

Date	Place	Rescue analgesics	Oxycodone (n=41)	Fentanyl (n=41)
POD0	PACU	Oxycodone or fentanyl*		
		Number of patients (n)	40	39
		Total amount (mg)	6 (4–6)	0.1 (0.07–0.1)
	Ward	Tramadol		
		N/ F/ A	2/3/0 (0–0)	5/7/0 (0–0)
		Pethidine		
		N/ F/ A	14/14/0 (0–25)	20/21/25 (0–25)
POD1		Tramadol		
		N/ F/ A	2/1/0 (0–0)	4/6/0 (0–0)
		Pethidine		
		N/ F/ A	2/2/0 (0–0)	3/4/0 (0–0)
POD2		Tramadol		
		N/ F/ A	1/1/0 (0–0)	3/3/0 (0–0)
		Pethidine		
		N/ F/ A	0/0/0 (0–0)	1/1/0 (0–0)

The data are expressed as count or median (25–75%) or count as appropriate. Those parameters were compared using Mann-Whitney rank sum test or chi-square test as appropriate. POD: postoperative day, PACU: postanesthesia care unit, N: Number of patients receiving rescue analgesics (n), F: frequency (n), A: total amount (mg). *: Oxycodone and fentanyl groups patients were given oxycodone and fentanyl as rescue analgesics at PACU, respectively. The oxycodone and fentanyl groups did not differ significantly in terms of any of the variables.

Table 4. Rhodes index of nausea vomiting retching (RINVR) and Modified Observer's Assessment of Alertness/Sedation (MOAA/S)

	Oxycodone (n=41)	Fentanyl (n=41)
RINVR		
POD1	0 (0–3)	0 (0–1)
POD2	0 (0–1)	0 (0–0)
MOAA/S		
PACU (5/4/3/2–0)	31/8/2/0	32/8/1/0
POD1 (5/4/3/2–0)	39/2/0/0	37/4/1/0
POD2 (5/4/3/2–0)	39/2/0/0	40/1/0/0

The date are expressed as median (25–75%) or count, as appropriate. POD: postoperative day, PACU: postanesthesia care unit. The two groups were compared in terms of RINVR and MOAA/S scores using Mann-Whitney U test or Chi-squared test, as appropriate.The groups did not differ significantly in terms of any of the variables.

Table 5. Time to minimum effective analgesic concentration (MEAC) and 90% steadystate (SS), and plasma concentration (Cp) at SS in intravenous patient-controlled analgesia with oxycodone

Loading dose	2 mg		0.1 $mg \cdot kg^{-1}$	
Background infusion of 10 mg/h	–	+	–	+
Time to MEAC, h	4	2.7	2.5	2
Time to 90% SS, h	11–16	11–16	9–14	9–14
Cp at SS, $ng \cdot ml^{-1}$	79–113	99–142	79–113	99–142

The data show the predicted oxycodone concentration in the plasma over time in hypothetical male and female subjects aged 19, 54, and 89 years after they receive an intravenous bolus of 2 mg or 0.1 $mg \cdot kg^{-1}$ followed by 1 mg demand boluses every 15 min with or without background infusion at 1 $mg \cdot h^{-1}$. The body weights and heights of all subjects are 60 kg and 165 cm, respectively.