

# Comparison of the effects of oxycodone versus fentanyl on airway reflex to tracheal extubation and postoperative pain during anesthesia recovery after laparoscopic cholecystectomy

## A double-blind, randomized clinical consort study

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### Abstract

**Background:** Fentanyl has been suggested to be effective for controlling airway and hemodynamic responses to tracheal extubation. This study was performed to compare the effects of oxycodone and fentanyl on airway and hemodynamic responses and postoperative pain during the recovery period in patients undergoing laparoscopic cholecystectomy.

**Methods:** Ninety patients aged 18 to 65 years were randomly allocated to 1 of 3 groups: fentanyl, oxycodone, and control. Coughing responses (incidence and severity), hemodynamic responses during the recovery period, and acute postoperative pain were assessed.

**Results:** The incidence of cough was decreased in the fentanyl and oxycodone groups compared with that in the control group at the points of awareness and extubation, and no significant difference was observed between the 2 treatment groups. Severe cough response was decreased in the fentanyl and oxycodone groups compared with that in the control group at the point of extubation, and no significant change was observed in cough severity between the 2 treatment groups. Postoperative pain scores were lower in the fentanyl and oxycodone groups than those in the control group at 5 and 30 minutes postoperatively, and no significant difference was observed between the 2 treatment groups. Hemodynamic responses did not differ among the 3 groups during the recovery period.

**Conclusion:** Oxycodone treatment before tracheal extubation reduced cough response and was as effective as fentanyl treatment for improving extubation quality. Furthermore, single boluses of fentanyl and oxycodone showed equal effectiveness in attenuating acute postoperative pain in patients undergoing laparoscopic cholecystectomy.

**Abbreviations:** BIS = bispectral index, HR = heart rate, MBP = mean blood pressure, NRS = numerical rating scale, PACU = postanesthetic care unit, TCI = target controlled infusion.

**Keywords:** fentanyl, laparoscopic cholecystectomy, oxycodone, tracheal extubation

## 1. Introduction

One of the major concerns related to tracheal extubation is prevention of respiratory complications such as coughing, laryngospasm, breath holding, desaturation, and pulmonary edema.<sup>[1]</sup> Moreover, tracheal extubation can cause hypertension

and tachycardia as a result of sympathetic stimulation.<sup>[2]</sup> Many drugs and techniques have been used to attenuate airway and hemodynamic responses with varying efficacy.

Fentanyl is a synthetic opioid that is commonly used to control moderate or severe pain. It has a rapid onset and provides 30 to 60 minutes of analgesia following a single intravenous injection,<sup>[3]</sup> making it useful for acute pain management during the perioperative period. In addition to this advantage, hemodynamic stability and a favorable recovery profile during and after extubation have been associated with the efficacy of fentanyl.<sup>[4,5]</sup>

Oxycodone is a strong semisynthetic opioid and although its onset time is similar to that of fentanyl, oxycodone has a longer analgesic duration (2–5 hours).<sup>[6]</sup> Recently, many studies have shown that the analgesic effects of oxycodone are better than those of fentanyl in treating postoperative pain.<sup>[7,8]</sup> Oxycodone has also been effectively utilized to attenuate hemodynamic changes during intubation.<sup>[9]</sup>

Therefore, we hypothesized that oxycodone could reduce airway responses and prevent detrimental hemodynamic changes following tracheal extubation as effectively or potentially more effectively than fentanyl. This study was performed to compare the effects of oxycodone and fentanyl on airway and hemodynamic responses and postoperative pain during the recovery period in patients undergoing laparoscopic cholecystectomy.

Editor: Chun-Yao Yang.

This work was supported by the 2017 Yeungnam University Research Grant.

The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:13(e0156)

Received: 7 July 2017 / Received in final form: 8 February 2018 / Accepted: 27 February 2018

<http://dx.doi.org/10.1097/MD.00000000000010156>

## 2. Materials and methods

### 2.1. Study population and anesthesia

This study was approved by the Institutional Review Board committee of the Yeungnam University Hospital, Daegu, Republic of Korea. Written informed consent was obtained from all the patients. This study was registered at clinicaltrials.gov (NCT03204045). We included patients aged 18 to 65 years with an American Society of Anaesthesiologists physical status classification of I or II who were scheduled for elective laparoscopic cholecystectomy. The exclusion criteria were allergies to either fentanyl or oxycodone, a history of chronic use of other opioids or analgesics, a history of smoking, a history of cardiac, hepatic, respiratory, or renal disease, current respiratory tract infection, other comorbid conditions, cognitive impairment, or a body mass index greater than 35 kg/m<sup>2</sup>.

The patients were assigned to 1 of 3 groups by computer-generated randomization: the fentanyl group, the oxycodone group, or the control group. None of the patients were premedicated. After applying routine hemodynamic monitoring (electrocardiography, noninvasive blood pressure, capnography, and pulse oximetry), general anesthesia was induced with propofol (1.5–2.5 mg/kg) and remifentanyl at an initial target concentration of 3 to 4 ng/mL using target-controlled infusion (TCI) devices (Orchestra Base Primea, Fresenius Vial, France). After intravenous injection of rocuronium (0.6–0.8 mg/kg), intubation was performed using an endotracheal tube with an internal diameter of 7.5 mm for females and 8.0 mm for males. Anesthesia was maintained with 6 to 9 vol% end-tidal concentration of desflurane in 50% oxygen with air and a continuous infusion of remifentanyl (fixed target concentration of 2–3 ng/mL), which were adjusted to maintain acceptable hemodynamic parameters and a bispectral index (BIS) of 40 to 60. When carbon dioxide gas was desufflated, desflurane was titrated to a 0.6 MAC, and remifentanyl was discontinued. After all surgical procedures were completed, desflurane was discontinued. Ten minutes prior to the completion of the operation, the patients received a 2 mL mixture of fentanyl (1 µg/kg) or oxycodone (0.08 mg/kg) in isotonic saline intravenously according to their allocated study groups by an anesthesiologist who was blinded to the group-treatment allocation. Residual neuromuscular blockade was antagonized by intravenous pyridostigmine (0.2 mg/kg) and glycopyrrolate (0.01 mg/kg). Oral suction was gently performed. Tracheal extubation was smoothly performed when the patients opened their eyes in response to a verbal request and spontaneous ventilation was adequate.

### 2.2. Study assessments

Airway reflex responses, including coughing, breath holding, bucking, and laryngospasm, were recorded at the point of awareness (eye opening in response to verbal commands), extubation, and 3 minutes after tracheal extubation. Hemodynamic responses were recorded at the completion of surgery (T1), at the point of awareness (T2), at the point of extubation (T3), and 3 min after tracheal extubation (T4). All assessment parameters were evaluated by a different anesthesiologist who was blinded to the group randomization. Extubation time (from discontinuation of desflurane until extubation) was recorded for all the patients.

Coughing severity was assessed using a 5-point scale (0 = no coughing; 1 = smooth extubation, minimal coughing (1–2 times); 2 = moderate coughing (3–4 times); 3 = severe coughing (5–10 times) and straining; 4 = poor extubation, very uncomfortable (laryngospasm and coughing > 10 times).<sup>[4]</sup> Scores of 3 and 4 were considered clinically severe. Breath holding was defined as desaturation and not breathing for ≥ 20 seconds, resulting in a > 5% decrease in SpO<sub>2</sub> from baseline. The mean blood pressure (MBP), heart rate (HR), and SpO<sub>2</sub> were also measured at the same time point.

In the recovery room, hemodynamic responses were evaluated every 5 minutes for 30 minutes. Postoperative pain intensity was assessed at 5 and 30 minutes in the postanesthetic care unit (PACU) using a numerical rating scale (NRS) ranging from 0 (no pain) to 10 (worst possible pain). When the pain score was ≥ 5 or the patient asked for rescue analgesics, 30 mg of ketorolac was injected intravenously. The sedation score was also recorded at the same time points using a scale of 1 to 5, where 1 indicates that the patient is asleep but easily roused, and 5 represents somnolent and minimal or no response to stimulation.<sup>[10]</sup> Any adverse reactions (nausea, vomiting, dizziness, hypotension, and respiratory depression) in the recovery room were also recorded. All data were assessed by an anesthesiologist who was blinded to the study.

### 2.3. Statistical analyses

Based on our preliminary study, the coughing response rate after laparoscopic cholecystectomy was 70%. A 50% reduction in the incidence of coughing responses in the fentanyl or oxycodone group was considered clinically relevant, and 30 patients were required per group ( $\alpha = 0.05$ , power = 80%). Therefore, 33 patients were selected for each group to account for dropouts. The data are expressed as numbers (%) or means (SD). Statistical analysis was performed using SPSS software (IBM, Chicago, IL). After assessing the normality of the data with the Shapiro–Wilk test and Kolmogorov–Smirnov test, categorical variables were analyzed using the  $\chi^2$  test or Fisher exact test, followed by Z tests with Bonferroni correction, and continuous variables were analyzed using ANOVA. A value of  $P < .05$  was considered statistically significant.

## 3. Results

Of the 99 enrolled patients, 90 were randomized into the 3 groups and were eligible for analysis; 4 did not meet the inclusion criteria, and 5 did not want to participate in the study (Fig. 1). No significant differences were found among the 3 groups with respect to demographic data and anesthetic characteristics of the patients (Table 1). The incidence of cough was significantly decreased in the fentanyl and oxycodone groups compared with that of the control group at the points of awareness ( $P = .039$  for both) and extubation ( $P = .028$  and  $P = .015$ , respectively), and no significant difference was observed between the fentanyl and oxycodone groups. The incidence of bucking and breath holding was not different among the 3 groups (Table 2). The severity of cough significantly differed among the 3 groups at the points of awareness and extubation ( $P = .035$  and  $P = .002$ , respectively). Post hoc tests with Bonferroni correction showed that the incidence of severe cough was lower in the oxycodone group than in the control group at the point of awareness and that the incidence of severe cough was decreased in the fentanyl and oxycodone groups compared with that in the control group at the

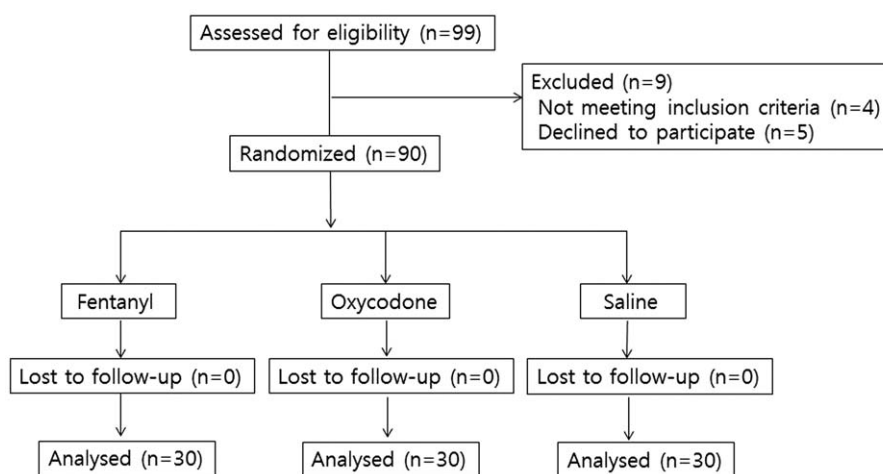


Figure 1. Flow diagram of the study design and patient selection.

point of extubation. No significant change was observed in cough severity between the fentanyl and oxycodone groups (Table 3). Hemodynamic responses did not differ among the 3 groups at any time points (T1–T5) during the recovery period (Fig. 2).

The postoperative pain score was significantly lower in the fentanyl and oxycodone groups than in the control group at 5 ( $P < .001$  for both) and 30 minutes postoperatively ( $P = .034$  and  $P = .002$ , respectively). The requirement for rescue analgesics was

greater in the control group than in the oxycodone group ( $P = .028$ ), but there was no difference between the fentanyl group and the control group (Table 4). The 3 groups did not show significant differences regarding the prevalence of dizziness, nausea, vomiting, and sedation. Respiratory depression did not occur in any of the groups (Table 5).

#### 4. Discussion

In this study, oxycodone treatment before tracheal extubation reduced the coughing response and was as effective as fentanyl treatment in relieving airway reflexes and improving extubation quality, without an accompanying increase in side effects. Furthermore, single bolus of fentanyl and oxycodone were found to have equal effectiveness in attenuating acute postoperative pain in patients undergoing laparoscopic cholecystectomy.

During recovery from general anesthesia, smooth emergence and hemodynamic stability are important. In particular, airway reflex caused by endotracheal extubation may elicit various

**Table 1**  
Demographic data.

	Group		
	Group F (n=30)	Group O (n=30)	Group C (n=30)
Age, yr	46 ± 11.8	49 ± 10.3	51 ± 7.9
Male/female, n	10/20	14/16	14/16
Weight, kg	68 ± 12.2	68 ± 12.6	65 ± 10.9
Height, cm	163 ± 9.0	165 ± 8.1	161 ± 8.2
Duration of surgery, min	35 ± 13.7	36 ± 12.1	36 ± 11.4
Duration of anesthesia, min	60 ± 15.1	61 ± 15.0	60 ± 13.3
Time of extubation, min	4.2 ± 1.9	4.9 ± 2.7	5.0 ± 2.5

Data were expressed as mean ± SD or number.

Group F = fentanyl group, Group O = oxycodone group, Group C = control group.

**Table 2**  
Extubation quality.

	Group		
	Group F (n=30)	Group O (n=30)	Group C (n=30)
At awareness			
Cough	11 (36.7)*	11 (36.7)*	19 (63.3)
Bucking	2 (6.7)	0 (0.0)	3 (10.3)
At extubation			
Cough	16 (53.3)*	15 (50.0)*	24 (80.0)
Bucking	3 (10.0)	0 (0.0)	4 (13.3)
At after extubation			
Cough	3 (10.0)	0 (0.0)	3 (10.0)
Bucking	0 (0.0)	0 (0.0)	0 (0.0)

Data were expressed as number (%) of patients.

Group F = fentanyl group, Group O = oxycodone group, Group C = control group.

\*  $P < .05$  compared with control group.

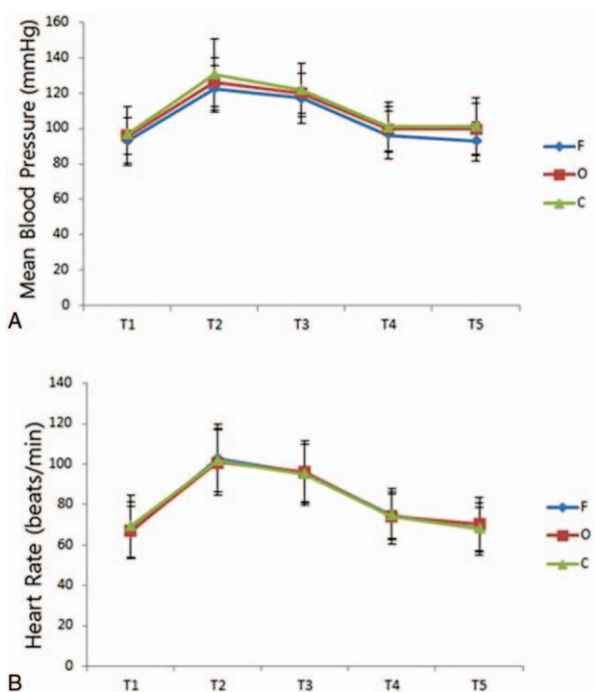
**Table 3**  
Cough severity.

	Group		
	Group F (n=30)	Group O (n=30)	Group C (n=30)
At awareness			
Cough none	19 (63.3)	18 (60.0)	11 (36.7)
Mild	4 (13.3)	9 (30.0)	4 (13.3)
Moderate	1 (3.3)	1 (3.3)	4 (13.3)
Severe	6 (20.0)	2 (6.7)*	11 (36.7)
At extubation			
Cough none	14 (46.7)	15 (50.0)	6 (20.0)
Mild	10 (33.3)	9 (30.0)	8 (26.7)
Moderate	6 (20.0)	3 (10.0)	4 (13.3)
Severe	0 (0.0)*	3 (10.0)*	12 (40.0)
At after extubation			
Cough none	27 (90.0)	30 (100.0)	27 (90.0)
Mild	2 (6.7)	0 (0.0)	2 (6.7)
Moderate	1 (3.3)	0 (0.0)	1 (3.3)
Severe	0 (0.0)	0 (0.0)	0 (0.0)

Data were expressed as number (%) of patients.

Group F = fentanyl group, Group O = oxycodone group, Group C = control group.

\*  $P < .05$  compared with control group.



**Figure 2.** Hemodynamic change in 3 groups. T1: completion of surgery; T2: point of extubation; T3: 3 min after tracheal extubation; T4 and T5: 5 and 30 min in PACU. F = fentanyl group, O = oxycodone group, C = control group.

complications such as coughing, bucking, breath holding, and laryngospasm,<sup>[1,11]</sup> and stimulation of the sympathetic nervous system can result in severe hypertension and tachycardia.<sup>[12]</sup> These distressing adverse events can significantly increase morbidity (airway obstruction, pulmonary edema, arrhythmia, myocardial ischemia, and surgical bleeding) and generate considerable costs (drugs, nursing cares, unanticipated reintubation, and delayed discharge). Deep extubation (defined as tracheal extubation while a patient is deeply sedated to blunt the laryngeal reflex) may be preferable to avoid these undesirable outcomes; however, this alternative technique may not be suitable for nonfasting patients due to the risk of aspiration or for patients undergoing airway surgeries due to potential airway complications.<sup>[2]</sup> Therefore, although various therapeutic strategies have been implemented to attenuate airway and hemodynamic responses during extubation, no treatment has been demonstrated to be completely successful.

During emergence, opioids have been widely used to attenuate the sympathetic stimuli of tracheal extubation and postoperative pain. Many studies have identified the analgesic effects of fentanyl

**Table 4**  
Severity of postoperative pain.

	Group		
	Group F (n=30)	Group O (n=30)	Group C (n=30)
Pain-VAS at 5 min in PACU	2.7 ± 1.96*	1.9 ± 1.12*	4.8 ± 1.96
Pain-VAS at 30 min in PACU	2.7 ± 1.86*	2.3 ± 1.47*	3.9 ± 1.87
Rescue analgesics (n/%)	5/16.7	3/10.0*	10/33.3

Data were expressed as mean ± SD or number (%).

Group F = fentanyl group, Group O = oxycodone group, Group C = control group, PACU = postanesthetic care unit.

\*  $P < .05$  compared with control group.

**Table 5**  
Incidence of adverse events.

	Group		
	Group F (n=30)	Group O (n=30)	Group C (n=30)
Dizziness	1 (3.3)	0 (0)	1 (3.3)
Nausea or vomiting	3 (10.0)	3 (10.0)	4 (13.3)
Respiratory depression	0 (0)	0 (0)	0 (0)
Sedation score > 2	0 (0)	0 (0)	0 (0)

Data were expressed as number (%) of patients.

Group F = fentanyl group, Group O = oxycodone group, Group C = control group.

and oxycodone on postoperative pain.<sup>[7,10,13]</sup> Koch et al<sup>[10]</sup> reported that oxycodone had a better analgesic effect than fentanyl on postoperative pain after laparoscopic cholecystectomy, while Xie et al showed that oxycodone was not superior to fentanyl in improving postoperative pain. However, studies comparing the 2 drugs in terms of hemodynamic effects and airway responses to tracheal extubation are rare. Fentanyl has a short onset time and high lipid solubility. Its analgesic effect peaks in 5 minutes, reflecting rapid and extensive redistribution in the body.<sup>[10,14]</sup> The timed administration of fentanyl can somewhat offset hemodynamic responses resulting from endotracheal intubation or extubation.<sup>[15,16]</sup> Oxycodone, a newly developed semisynthetic opioid, is structurally analogous to morphine, with 1:1 analgesic strength in controlling postoperative pain.<sup>[17]</sup> The onset time of oxycodone is similar to that of fentanyl; however, it has a longer duration of action compared with fentanyl.<sup>[6]</sup> Lee et al<sup>[9]</sup> showed that oxycodone and fentanyl comparably attenuated the hemodynamic response following endotracheal intubation during surgery for nasal bone fracture. The present study showed that fentanyl (1 μg/kg) and oxycodone (0.08 mg/kg) had no attenuating effect on increases in BP and HR following extubation. The treatment doses of the 2 drugs may have been insufficient to maintain hemodynamic stability. However, regarding postoperative pain control, the clinical efficacy of oxycodone was comparable to that of fentanyl at equianalgesic doses.

Among the various airway reflex responses related to the presence of an endotracheal tube, coughing is the most common.<sup>[18]</sup> The cough reflex during emergence from anesthesia is evoked by the activation of the ascending vagus nerve in the airway by chemical and mechanical irritations.<sup>[19]</sup> Coughing on emergence is a physiologic airway reflex, and appropriate activation of the cough reflex may have a protective effect in terms of prevention of aspiration and airway obstruction during breathing. However, coughing can induce serious complications such as cardiovascular instability, bleeding at the surgical site, laryngospasm, and increased intracranial and intrathoracic pressure, which can cause detrimental effects. Therefore, various medications are used (lidocaine, propofol, dexmedetomidine, and remifentanyl) to inhibit coughing during anesthetic recovery.<sup>[20–23]</sup> Short-acting opioids are widely used for smooth extubation, and recent studies have reported that fentanyl administration resulted in a more comfortable emergence and recovery.<sup>[5,16,24]</sup> Conversely, fentanyl-induced cough can be harmful to patients, although it is mostly transient and limited.<sup>[25,26]</sup> This adverse event occurs frequently following anesthetic induction with high doses (greater than 2 μg/kg intravenously) of fentanyl and rapid injection rates. Therefore, we elected to administer fentanyl (1 μg/kg intravenously) to suppress airway irritation during anesthetic emergence, and compared its effects with those of oxycodone. To the best of our knowledge, no studies have reported the effect of oxycodone on



attenuating the cough response to tracheal extubation. In this study, a single dose of oxycodone was as effective as fentanyl in attenuating airway reflexes during recovery from general anesthesia, although the mechanism of the beneficial effects of fentanyl and oxycodone on airway reflex remains unknown.

While opioid drugs may be useful for facilitating smooth emergence, they are associated with additional side effects such as delayed emergence, sedation, dizziness, nausea, vomiting, and respiratory depression. In this study, no difference in the incidence of side effects was observed between the 2 treatment groups or between the treatment groups and the control group.

This study has some limitations. First, we used only a single dose of fentanyl or oxycodone to compare their effects on the cough response with tracheal extubation. The results did not have sufficient power to compare the differences between 2 drugs. Therefore, further studies involving timed titrations are required. Second, the sample size of this study was determined from the results of the power analysis in the planning stage of the study. However, if additional subjects had been enrolled for analysis, the effects of fentanyl and oxycodone on airway reflexes and hemodynamic responses could have been assessed more accurately. Third, we analyzed the data of the patients who eventually completed the study rather than the data of all initially enrolled patients. Intention-to-treat analysis, which involves the randomization of all participants, required for more conservative estimates to avoid various misleading biases. Fourth, the emergence response varies based on type of operation, and our results were limited to laparoscopic cholecystectomy. Therefore, cough suppression effects of fentanyl and oxycodone during tracheal extubation may not be generalizable to patients undergoing different procedure. Finally, the airway reflex assessment was limited to the first 3 minutes after extubation. Though adverse respiratory events typically occur shortly afterward tracheal extubation, a longer time interval should be considered for observation during recovery.

In conclusion, oxycodone and fentanyl were found to be beneficial for attenuating airway reflexes in response to tracheal extubation and for relieving immediate postoperative pain in patients undergoing laparoscopic cholecystectomy.

## Author contributions

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