JCS Journal of Chest Surgery
https://doi.org/10.5090/jcs.20.136
pISSN: 2765-1606 eISSN: 2765-1614
J Chest Surg. 2021;54(3):200-205

Clinical Research

Fentanyl versus Remifentanil for Cough Suppression and Recovery after Video-Assisted Thoracic Surgery

Hee Won Son, M.D.[1], Ji Min Lee, M.D.[2], Se Hun Park, M.D., Ph.D.[1], Yong Jic Lee, M.D., Ph.D.[2], Ji Mi Oh, M.D.[1], Su Kyung Hwang, M.D., Ph.D.[2]

Departments of [1]Anesthesiology and Pain Medicine and [2]Thoracic and Cardiovascular Surgery, Ulsan University Hospital, Ulsan, Korea

ARTICLE INFO
Received October 12, 2020
Revised December 8, 2020
Accepted December 21, 2020

Corresponding author
Su Kyung Hwang
Tel 82-52-250-7140
Fax 82-52-250-8558
E-mail victorylina@gmail.com
ORCID
https://orcid.org/0000-0003-2759-2774

Background: Various methods have been used to reduce postoperative pain after thoracic surgery. However, these methods may affect the patient's respiratory response and delay recovery from anesthesia. We aimed to evaluate the effects of fentanyl and remifentanil during extubation after video-assisted thoracic surgery (VATS).
Methods: This study included 45 randomly-selected male patients who underwent VATS for pneumothorax between July 2011 and August 2012. We divided the participants into 3 groups: the F group, which received a bolus injection of 1.0 μg/kg of fentanyl; the R1 group, which received a 0.04 μg/kg/min remifentanil infusion; and the R2 group, which received a 0.08 μg/kg/min remifentanil infusion. Hemodynamics, pain, cough, consciousness level, and nausea were assessed for each group.
Results: The number and severity of coughs were lower in the R1 and R2 groups than in the F group, and there were no differences between the R1 and R2 groups. Respiratory depression and loss of consciousness were not observed in any of the patients, and there were no differences in hemodynamics.
Conclusion: In comparison with fentanyl, remifentanil did not result in a wide fluctuation of blood pressure and heart rate upon emergence from general anesthesia. Moreover, remifentanil contributed to cough suppression and postoperative pain control. Remifentanil seems to be a safe and effective analgesic after VATS.

Keywords: Anesthesia, Cough, Fentanyl, Remifentanil, Thoracic surgery

Introduction

Thoracic surgery causes postoperative pain due to the nature of the procedure and leads to accumulated secretions in the lungs. Therefore, severe coughing due to bronchial irritation upon emergence from anesthesia is commonly observed; chest pain at the surgical site may also cause dyspnea and instability, leading to emergence from anesthesia. Coughing during emergence is caused by branchial stimulation, and may result in high blood pressure, elevated brain pressure, tachycardia, arrhythmia, or bleeding at the surgical site [1-3]. Several studies have reported that intravenous fentanyl is beneficial for hemodynamic and airway-response safety during extubation [4,5]. Other studies have shown that continuous intravenous administration of remifentanil provided the benefits of rapid onset and fast recovery without accumulation after stopping administration [6-8] and that it reduces the aforementioned side effects [9,10]. However, there is a general opinion that remifentanil administration, which provides continuous pain control, may delay a patient's emergence from anesthesia when compared to temporary fentanyl administration. In the study, we evaluated the effects of temporary administration of fentanyl and continuous administration of remifentanil on airway stability, the emergence of patients from anesthesia, and postoperative pain during extubation after video-assisted thoracic surgery (VATS).

Methods

This study was conducted after receiving approval from the Institutional Review Board of Ulsan University Hospi-

tal (approval no., 2011-031), and written informed consent was obtained from all patients. It included men between 16 and 30 years of age with an American Society of Anesthesiologists score of 1 or 2 who underwent VATS for pneumothorax from July 2011 to August 2012. Patients with respiratory diseases, difficult airways, hypertension, diabetes, heart disease, liver disease, or kidney disease were excluded from the study. We used G*Power ver. 3.1.9.2 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany; http://www.gpower.hhu.de/) and referred to the study of Gesztesi et al. [11] to calculate the sample size using a standardized effect size (α=0.05 and β=0.3). The resulting sample size was 15 patients per group. Patients were randomly selected and assigned to each group by a computer program until 15 patients were included in each group.

After the patients arrived at the operating room, vital signs were measured using a non-invasive automatic sphygmomanometer, electrocardiogram, pulse oximeter, and thermometer. Patients were divided into 3 groups: the F group, which received an intravenous bolus of fentanyl (1.0 μg/kg); the R1 group, which received a 0.04 μg/kg/min infusion of remifentanil (Model AS50 Infusion Pump; Baxter, Deerfield, IL, USA); and the R2 group, which received a 0.08 μg/kg/min infusion of remifentanil (R2 group).

Anesthesia induction was performed with continuous administration of remifentanil (0.15 μg/kg/min) and sequential injection of thiopental (5 mg/kg), 2% lidocaine (1 mg/kg), and rocuronium (0.8 mg/kg). The size of the tube used for tracheal intubation differed depending on the height of the patient; specifically, 35F (Mallinckrodt Endobronchial Tube; Covidien, Dublin, Ireland), 37F, and 39F tubes were used for those less than 160 cm tall, 160–180 cm tall, and 180 cm or taller, respectively. Each of the tracheal and bronchial air sacs was filled with air using a manometer until a pressure of 20 mm Hg was reached. To maintain anesthesia, remifentanil (0.1 μg/kg/min) was continuously administered, and the concentration of sevoflurane was controlled between 1.0% and 3.0% to maintain systolic blood pressure and heart rate during surgery within 20% of the pre-anesthesia state. The anesthesia machine was set to inject 4 L/min of 100% oxygen and to maintain end-tidal CO_2 at 30 mm Hg to control tidal volume and the number of breaths per minute.

Once suturing began, the sevoflurane concentration was lowered to 0.5%, and ondansetron (4 mg) was intravenously administered for anti-vomiting purposes. After suturing was completed, remifentanil injection was stopped in the F group, and fentanyl (1.0 μg/kg) was administered. In the R1 and R2 groups, the injection rate of remifentanil was adjusted to 0.04 μg/kg/min and 0.08 μg/kg/min, respectively, for continuous administration. With the patient in the supine position, sevoflurane injection was stopped, and mechanical breathing was switched to spontaneous breathing. The patient's name was called every 30 seconds to encourage the patient to open his eyes. If the train of four (TOF) ratio was 0.8 or higher in the muscle acceleration test (TOF-Watch; Organon Ltd., Dublin, Ireland), 15 mg of pyridostigmine and 0.4 mg of glycopyrrolate were administered. Extubation was performed when spontaneous breathing was more than 15 times per minute but less than 30 times per minute, respiratory volume was more than 5 mL/kg, and the patient could follow simple verbal instructions. After extubation, the patient was moved to the recovery room when the tidal volume was measured to be over 8 mL/kg while wearing an anesthetic mask. The time intervals from inhalation stopping until the patient opened his eyes (after being prompted), until anesthesia injection stopped, and until extubation of the tracheal tube were measured. In addition, the number and severity of coughs before extubation of the tracheal tube were measured, as were the number and severity of coughs from after extubation until arrival in the recovery room. All patient groups were anesthetized by a single skilled anesthesiologist, and all measurements were evaluated by a single anesthesiologist, who did not participate in anesthesia. Patients in the R1 and R2 groups received continuous administration of their respective concentrations of remifentanil until 10 minutes before leaving the recovery room.

The severity of coughs was measured using the 3-category scale established by Minogue et al. [12]. One cough was recorded as mild. Continuous coughing that lasted no more than 5 seconds and continuous coughing that lasted more than 5 seconds were recorded as moderate and severe, respectively. Blood pressure and heart rate were measured before the induction of anesthesia, before extubation, after extubation, and 5 minutes after extubation. The presence or absence of respiratory depression, level of consciousness and presence or absence of loss of consciousness, severity of pain, severity of nausea and vomiting, number of additional analgesic administrations, and time spent in the recovery room were recorded until the patient left the recovery room. If percutaneous oxygen saturation was less than 95% for more than 5 minutes, the patient was considered to have respiratory depression. The Riker Sedation-Agitation Scale was used to assess the patient's level of consciousness, and a score of 3 or less was evaluated as a loss of consciousness [13]. Severity of pain and severity of nausea were measured using a Visual Analog Scale (VAS).

No pain or nausea was recorded as 0 points, and unbearable pain or nausea was given 10 points. If respiratory depression or loss of consciousness was observed, the administration of remifentanil was discontinued and appropriate measures were taken. If the pain VAS score was 8 or higher, fentanyl (0.5 μg/kg) was administered. Additional fentanyl (0.5 μg/kg) was administered as necessary for pain control. The traditional Aldrete scoring system was used to assess if the patient was well enough to leave the recovery room.

Categorical variables were analyzed using the Fisher exact test, and continuous variables using the Kruskal-Wallis test. Hemodynamic variables were analyzed using repeated-measures analysis of variance. All statistical analyses were performed using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA), and p-values less than 0.05 were considered to indicate statistical significance.

Results

No significant differences in age, operation time, weight, and anesthesia time were observed among the groups (Table 1). Blood pressure and heart rate increased in all 3 groups when extubation was performed, and no significant differences were observed among the groups (p=0.176 for systolic blood pressure; p=0.435 for diastolic blood pressure; p=0.196 for heart rate) (Fig. 1A–C).

The details of patients' recovery profile are summarized in Table 2. No significant differences were found among the groups in the time until the patient opened his eyes after stopping the anesthesia injection (p=0.251) or in the time until extubation after sevoflurane was discontinued (p=0.262). The number and severity of coughs were lower in the R1 and R2 groups than in the F group (p<0.05). Moreover, the level of consciousness after arriving in the recovery room did not significantly differ among the groups (p=0.25). The pain scores after arrival in the recovery room and 5 minutes before leaving the recovery room were lower in the R2 group than in the F group (p=0.040). In addition, the frequency of analgesic administrations was highest in the F group (p=0.002). The nausea score was higher in the R1 group than in the R2 group, but without statistical significance (p=0.105)

Respiratory depression and loss of consciousness were not observed in any of the patients, and there were no differences among the groups in the departure time from the recovery room.

Discussion

Coughing during emergence from general anesthesia should be avoided, as it can cause various side effects such as high blood pressure, elevated brain pressure, tachycardia, arrhythmia, and bleeding at the surgical site. Coughs are triggered by the cough reflex, which is induced by organ stimulation. Rapidly adapting receptors distributed in the epithelium of organs with Aδ fibers receive stimuli and transmit signals to the central nervous system, leading to coughing. Coughs can be reduced using local anesthetics to suppress peripheral nerve irritation, opioid agents that act on the central nervous system, and GABA (gamma-aminobutyric acid) receptor agonists [14]. Opioid agents mainly signal through μ-opioid receptors [15]. Opioid agents not only suppress coughing, but also reduce excitatory emergence and contribute to hemodynamic stability. Thus, opioid agents have been used widely for emergence from general anesthesia in recent years [16].

Remifentanil, which is a 4-aniline-piperidine derivative, is a selective agonist that acts on μ-opioid receptors with a rapid onset of action. Thus, it is useful for rapid anesthesia induction. Remifentanil contains two methyl-ester bonds and is rapidly removed by non-specific esterase in blood and tissues, resulting in a final half-life of less than 10 minutes. Moreover, its context-sensitive half-time is approximately 3 minutes, regardless of the time of injection. Therefore, remifentanil is relatively safe, even after repeated administration or long-term use [15,17,18]. It has been reported that continuous administration of low-dose

Table 1. Patients' characteristics

Characteristic	Fentanyl group (n=15)	Remifentanil group 1 (n=15)	Remifentanil group 2 (n=15)	p-value
Age (yr)[a]	17.85±1.12	18.25±2.10	20.25±5.38	0.937
Body weight (kg)[a]	60.42±9.17	55.12±14.86	56.97±18.80	0.465
Height (cm)[a]	176.43±5.31	172.63±9.77	170.25±8.21	0.565
Operation time (min)[a]	44.28±3.19	46.43±15.05	36.88±15.95	0.675
Left-side pneumothorax[b]	5	6	4	0.866

Values are presented as mean±standard deviation or number.
[a]Statistical significance was tested using the Kruskal-Willis test of variance among groups. [b]Statistical significance was tested using the Fisher exact test.

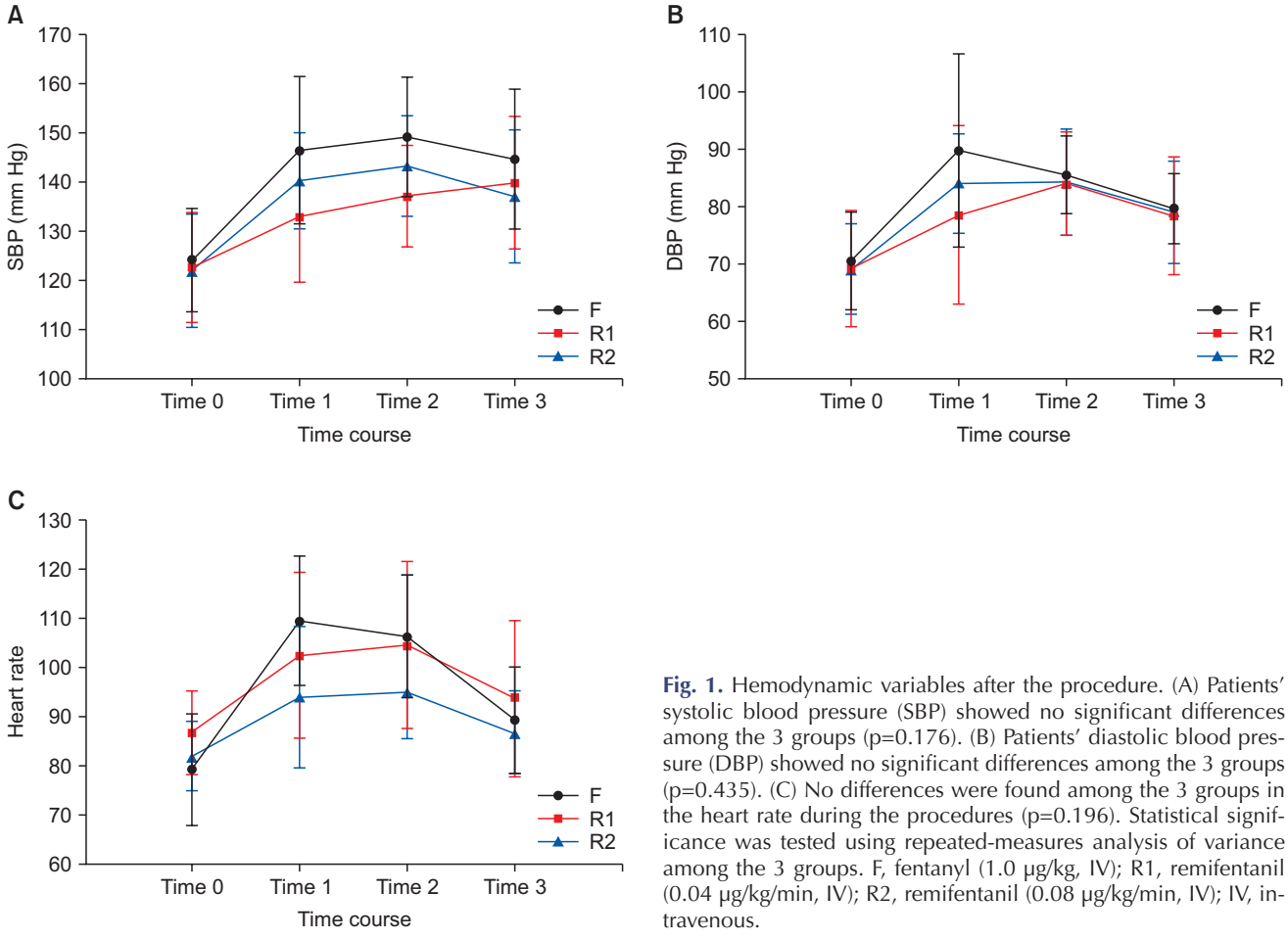

Fig. 1. Hemodynamic variables after the procedure. (A) Patients' systolic blood pressure (SBP) showed no significant differences among the 3 groups (p=0.176). (B) Patients' diastolic blood pressure (DBP) showed no significant differences among the 3 groups (p=0.435). (C) No differences were found among the 3 groups in the heart rate during the procedures (p=0.196). Statistical significance was tested using repeated-measures analysis of variance among the 3 groups. F, fentanyl (1.0 μg/kg, IV); R1, remifentanil (0.04 μg/kg/min, IV); R2, remifentanil (0.08 μg/kg/min, IV); IV, intravenous.

Table 2. Recovery profiles by group

Variable	Fentanyl group[a]	Remifentanil group 1[b]	Remifentanil group 2[c]	p-value	Post hoc (Scheffé)
Time to eye opening (min)[a)]	318.27±186.709	351.20±90.518	388.10±136.962	0.251	-
Time to extubation (min)[a)]	384.55±183.669	434.00±87.933	454.90±155.082	0.262	-
No. of coughs[a)]	4.64±1.362	1.30±1.252	0.90±0.738	0.000	b,c<a
Cough grade[b)]				0.003	
0	0	4 (40.0)	3 (30.0)		
1	2 (18.2)	4 (40.0)	7 (70.0)		
2	4 (36.4)	1 (10.0)	0		
3	5 (45.5)	1 (10.0)	0		
Level of consciousness[b)]				0.25	
3	1 (9.1)	4 (40.0)	2 (20.0)		
4	8 (72.7)	6 (60.0)	8 (80.0)		
5	2 (18.2)	0	0		
Pain (VAS score)[a)]	7.09±2.548	5.40±2.716	3.60±2.271	0.040	c<a,b
Nausea (VAS score)[a)]	5.55±1.508	4.90±1.853	3.40±2.271	0.060	-
Additional opioid administrations[a)]	1.91±1.136	0.80±0.789	0.40±0.422	0.002	b,c<a

Values are presented as mean±standard deviation or number (%).
VAS, Visual Analog Scale.
[a)]Statistical significance was tested using the Kruskal-Willis test of variance among groups. [b)]Statistical significance was tested using the Fisher exact test.

remifentanil in critically ill patients on artificial ventilation can provide adequate stability, breathing, and stable hemodynamic conditions [19]. After administration of anesthetics during extubation of the endotracheal tube, the patient should be able to recover the protective reflex mechanism within a short period of time. Moreover, the anesthetics should not induce prolonged hypotension or respiratory depression. The pharmacological properties of remifentanil satisfy these conditions, and many studies have shown its effects on hemodynamic stability during intubation [20,21].

This study compared the effects of fentanyl and remifentanil, the 2 most popular opioid agents used recently, on emergence from general anesthesia. Fentanyl was intravenously administered in a temporary manner, while remifentanil was continuously administered. We did not intend to compare the effects due to differences in the pharmacokinetic and pharmacological properties of the 2 drugs. Instead, we aimed to evaluate the differences observed during recovery and extubation, including the different methods of administration. In particular, remifentanil offers several advantages, such as hemodynamic stability and cough suppression. However, remifentanil has also been known to delay recovery. Thus, differences among the 3 groups in the time until the patient opened his eyes after stopping the anesthesia injection and the time until extubation of the tracheal tube were carefully observed.

As noted above, there were no significant differences among the groups in the time until the patient opened his eyes after stopping the anesthesia injection or in the time until extubation of the tracheal tube. The R1 and R2 groups showed significantly better results in the number and severity of coughs, postoperative pain scores, and number of additional analgesic administrations than the F group, and the R2 group showed significantly better results than the R1 group. Therefore, continuous administration of remifentanil may be more helpful than temporary intravenous administration of fentanyl for maintaining a stable state during extubation. Interestingly, there were no significant differences in blood pressure or heart rate among the 3 groups. As seen in previous studies, opioid agents contributed to hemodynamic stability during intubation, and temporary administration of fentanyl may have demonstrated effects comparable to continuous administration of remifentanil.

There are several limitations of this study. First, a control group that did not receive drugs was not established. However, previous studies have already demonstrated that the use of drugs contributed to emergence from anesthesia, cough suppression, and hemodynamic stability during extubation when compared to an untreated group [10,22]. Moreover, this study aimed to assess the differences between temporary administration of fentanyl and continuous administration of remifentanil. This is why we did not include a control group that did not receive drugs. A second limitation relates to the dosages of the medications that were analyzed. In particular, it is unknown whether the same results would have been observed if a higher dose of fentanyl had been used. Moreover, the remifentanil experimental group was divided into 2 groups, R1 (0.04 μg/kg/min) and R2 (0.08 μg/kg/min). As better results were observed in the R2 group, it seems necessary to assess the results of higher doses of fentanyl as well. Contrary to concerns at the beginning of the study, side effects such as loss of consciousness and difficulty breathing were not observed in the R2 group. Although this issue is difficult to determine, continuous administration of higher doses of remifentanil is possible. Further studies are needed to pinpoint the optimal rate of administration for remifentanil. Lastly, the number of patients in the study groups was limited. Moreover, these patients with pneumothorax were relatively young and healthy. A study conducted with more patients would provide more reliable data.

In conclusion, continuous administration of remifentanil did not lead to any delay in emergence from general anesthesia when compared to temporary administration of fentanyl, and remifentanil contributed to cough suppression and postoperative pain control. Moreover, remifentanil was not inferior in terms of its hemodynamic profile. Remifentanil is feasible and effective for recovery after VATS.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

ORCID

Hee Won Son: https://orcid.org/0000-0002-8035-062X
Ji Min Lee: https://orcid.org/0000-0001-9317-0313
Se Hun Park: https://orcid.org/0000-0003-2264-4627
Yong Jic Lee: https://orcid.org/0000-0002-0837-4336
Ji Mi Oh: https://orcid.org/0000-0002-2365-0642
Su Kyung Hwang: https://orcid.org/0000-0003-2759-2774

References

1. Gonzalez RM, Bjerke RJ, Drobycki T, et al. *Prevention of endotra-*

cheal tube-induced coughing during emergence from general anesthesia. Anesth Analg 1994;79:792-5.
2. Bidwai AV, Bidwai VA, Rogers CR, Stanley TH. *Blood-pressure and pulse-rate responses to endotracheal extubation with and without prior injection of lidocaine*. Anesthesiology 1979;51:171-3.
3. Leech P, Barker J, Fitch W. *Proceedings: changes in intracranial pressure and systemic arterial pressure during the termination of anaesthesia*. Br J Anaesth 1974;46:315-6.
4. Nishina K, Mikawa K, Maekawa N, Obara H. *Fentanyl attenuates cardiovascular responses to tracheal extubation*. Acta Anaesthesiol Scand 1995;39:85-9.
5. Mendel P, Fredman B, White PF. *Alfentanil suppresses coughing and agitation during emergence from isoflurane anesthesia*. J Clin Anesth 1995;7:114-8.
6. Glass PS, Hardman D, Kamiyama Y, et al. *Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: remifentanil (GI87084B)*. Anesth Analg 1993;77:1031-40.
7. Egan TD. *Remifentanil pharmacokinetics and pharmacodynamics: a preliminary appraisal*. Clin Pharmacokinet 1995;29:80-94.
8. Michelsen LG, Hug CC Jr. *The pharmacokinetics of remifentanil*. J Clin Anesth 1996;8:679-82.
9. Lee B, Lee JR, Na S. *Targeting smooth emergence: the effect site concentration of remifentanil for preventing cough during emergence during propofol-remifentanil anaesthesia for thyroid surgery*. Br J Anaesth 2009;102:775-8.
10. Nho JS, Lee SY, Kang JM, et al. *Effects of maintaining a remifentanil infusion on the recovery profiles during emergence from anaesthesia and tracheal extubation*. Br J Anaesth 2009;103:817-21.
11. Gesztesi Z, Rego MM, White PF. *The comparative effectiveness of fentanyl and its newer analogs during extracorporeal shock wave lithotripsy under monitored anesthesia care*. Anesth Analg 2000;90:567-70.
12. Minogue SC, Ralph J, Lampa MJ. *Laryngotracheal topicalization with lidocaine before intubation decreases the incidence of coughing on emergence from general anesthesia*. Anesth Analg 2004;99:1253-7.
13. Riker RR, Fraser GL, Cox PM. *Continuous infusion of haloperidol controls agitation in critically ill patients*. Crit Care Med 1994;22:433-40.
14. Kamei J. *Role of opioidergic and serotonergic mechanisms in cough and antitussives*. Pulm Pharmacol 1996;9:349-56.
15. Beers R, Camporesi E. *Remifentanil update: clinical science and utility*. CNS Drugs 2004;18:1085-104.
16. Yarmush J, D'Angelo R, Kirkhart B, et al. *A comparison of remifentanil and morphine sulfate for acute postoperative analgesia after total intravenous anesthesia with remifentanil and propofol*. Anesthesiology 1997;87:235-43.
17. Hughes MA, Glass PS, Jacobs JR. *Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs*. Anesthesiology 1992;76:334-41.
18. Schmidt J, Hering W, Albrecht S. *Total intravenous anesthesia with propofol and remifentanil: results of a multicenter study of 6,161 patients*. Anaesthesist 2005;54:17-28.
19. Cavaliere F, Antonelli M, Arcangeli A, et al. *A low-dose remifentanil infusion is well tolerated for sedation in mechanically ventilated, critically-ill patients*. Can J Anaesth 2002;49:1088-94.
20. Thompson JP, Hall AP, Russell J, Cagney B, Rowbotham DJ. *Effect of remifentanil on the haemodynamic response to orotracheal intubation*. Br J Anaesth 1998;80:467-9.
21. Hwang JH, Kim YH, Lee JH, et al. *Comparison of effects of fentanyl, alfentanil and remifentanil on the cardiovasuclar response to endotracheal intubation during the induction of general anesthesia*. Korean J Anesthesiol 2008;54:18-24.
22. Inoue Y, Koga K, Sata T, Shigematsu A. *Effects of fentanyl on emergence characteristics from anesthesia in adult cervical spine surgery: a comparison of fentanyl-based and sevoflurane-based anesthesia*. J Anesth 2005;19:12-6.