Background: Remifentanil infusion is commonly used for general anesthesia but reflex cough can occur after an intravenous (IV) infusion. This study was designed to examine the effect of IV-dexamethasone on remifentanil-induced cough (RIC).

Methods: One hundred thirty patients scheduled for elective surgery were randomly assigned into two groups that received by either 2 ml of IV 0.9% saline (Group C, n = 68) or 10 mg of dexamethasone (Group D, n = 62) 5 min before administration of remifentanil at a target effect-site concentration of 5 ng/ml. The incidence and severity of coughs of each patient were recorded.

Results: The overall incidence of cough was 6.5% (4/62 patients) in Group D and 26.5% (18/68 patients) in the Group C (P = 0.002). The severity of cough observed was significantly different by dexamethasone pretreatment (P = 0.02) but there were no significant hemodynamic changes.

Conclusions: Pretreatment with dexamethasone after IV administration was effective in suppressing the reflex cough induced by remifentanil infusion. (Korean J Anesthesiol 2011; 60: 403-407)

Key Words: Cough, Dexamethasone, Remifentanil.

Introduction

Remifentanil is a fentanyl derivative and a μ-opioid receptor agonist with a very short reaction time. It has been shown that during induction of general anesthesia, and tracheal intubation, opioids suppress the cough reflex. Similar to fentanyl, the injection of remifentanil induces cough (i.e. remifentanil-induced cough, RIC), and the incidence has been reported to be approximately 27–28% [1,2].

Cough induced during the induction of general anesthesia sometimes, elevates cerebral, ocular or abdominal pressure, and thus it may become threatening to the patients. Tweed and Dakin [3], have reported the cases requiring immediate tracheal intubation for excessive coughs prior to the induction of general anesthesia.

Until now, efforts have been made to reduce the cough reflex...
induced by opioids agonists, and it has been reported that the selective β-2 agonist turbutaline or salbutamol, lidocaine, and ketamine were effective on reducing fentanyl-induced cough (FIC) or RIC [1,2,4-6]. In addition, Lim et al. [7] have reported that a split-dose intravenous injection of remifentanil reduced the incidence of cough, and Lin et al. [8] have reported that the pretreatment with dexamethasone reduced FIC effectively.

There are no studies on the incidence or severity of RIC in cases when patients are pretreated with the intravenous injection of dexamethasone.

Therefore, in our study, the incidence and severity of RIC was examined when patients were pretreated with 10 mg of dexamethasone, IV prior to the injection of remifentanil.

**Materials and Methods**

This study was approved by the Institutional Review Board. The purpose and methods of the study were explained sufficiently to patients and their guardians and then, consent was obtained for the study.

The study was conducted on 140 patients between the age of 18 years and 70 years with an Anesthesiologists Physical Status I and II.

Patients with a past history of smoking, chronic obstructive lung diseases, asthma or upper respiratory infection, a history of angiotensin converting enzyme inhibitor, bronchodilators, or steroid uses, or the history of allergy to drugs were excluded from our study. The patients fasted for 8 hours prior to surgery. A 20 G cannula was installed on the dorsum manus prior to the arrival in the operation rooms, and a T-connector was connected for drug injection. Midazolam (2 mg) and glycopyrrolate (0.2 mg) were injected intramuscularly 30 minutes prior to the injection of dexamethasone.

For all patients arriving in the operating room, an electrocardiogram, non-invasive blood pressure, and pulse oximetry were performed and the vital signs of patients were measured. A total of 140 patients were considered, but 10 patients dropped out and, 130 patients were then randomly assigned to either the control group (Group C) or the dexamethasone group (Group D). Five minutes prior to the injection of remifentanil, 10 mg of dexamethasone (in 2 ml total volume) was injected into patients in D group, and the same volume of 0.9% saline was injected into patients in group C.

Remifentanil was injected until the concentration reached the target concentration 5 ng/ml. Blood pressure of patient, pulse, and oxygen saturation levels were recorded immediately after arrival at operation room (T0), immediately after remifentanil reached the target concentration (T1), and after the injection of propofol (T2). The interval between T0 and T1 varied depending on the preparation process and the time to reach the target concentration for each patient: this time, was approximately 5–10 minutes, and thus T2 was measured 5 minutes after the measurement of T1.

The severity of cough was graded depending on the frequency of cough, and was recorded as mild (1–2 times), moderate (3–4 times), or severe (more than 5 times). A preliminary study was performed on 30 patients, and it was found that the cough reflex developed from the infusion of remifentanil to within 2 minutes after reaching the target concentration 5 ng/ml. Based on this, 2 minutes after reaching the target concentration was determined as the time for the injection of propofol.

During the injection of remifentanil, if oxygen saturation level decreased to lower than 90%, mask ventilation support using 100% oxygen was initiated immediately, and the development of apnea, stiffness of chest muscles, or neuropsychological symptoms were recorded. Apnea was defined as the respiration arrest period of longer than 20 seconds. Neuropsychological symptoms were defined as a the feeling of the dissociation phenomenon (i.e. as if the body is floating), impairment of alertness including drowsiness, changes of tastes, and changes of sensation such as numbness, hot, cold, etc..

In preliminary studies, the incidence of cough in the dexamethasone group was reduced by approximately 20% when compared to the saline injected control group. Using these data, the number of samples to obtain 80% statistical power at the 95% significance level was calculated as minimal 59 patients per group. Considering a drop out rate of approximately 10%, studies were attempted to be performed with a total sample number of 140 patients. For statistical analysis, SPSS 13.0 (SPSS Inc, Chicago, IL, USA) was used. All results were presented as a mean ± standard deviation. Comparison of age, height, weight, total amount of remifentanil, and hemodynamic measurements were analyzed by t-test. The comparison of the gender of the two groups, ASA class, with or without development of cough, and the severity of cough were analyzed by chi-square test. In all cases, a P value less than 0.05 was considered statistically significant.

**Results**

Out of 140 patients; that entered the study, 10 patients; had blockage of the intravenous line and thus were excluded from the study. Hence, a total 130 patients were enrolled as study patients and 68 patients were randomized in group
C and, and the 62 patients were randomized into group D. In any patient during the injection of remifentanils, there was never a development of the stiffness of chest muscles or neuropsychological symptoms and oxygen saturation level during the injection never decreased below 90%.

When comparing demographic data of the patients in both groups, age, gender, height, weight and ASA class were not different. Similarly, the total injection volume of remifentanil to reach the target concentration of 5 ng/ml in the two groups was not different (Table 1).

The vital signs assessed at the three designated time points (T0; immediately after arriving at operation room, T1; immediately after reaching the target concentration of remifentanil, T2; after the injection of propofol) of the two groups were also not different.

The development of cough observed from the time of the injection of remifentanil in Group C occurred in 18 patients (26.5%). Among them, 7 patients (38.9%) were classified as mild (1–2 times), 7 patients (38.9%) were moderate (3–4 times), and 4 patients (22.2%) were severe (more than 5 times). In Group D, cough developed in 4 patients (6.5%). Among them, 2 patients (50%) were mild, 2 patients (50%) were moderate, severe cough was not observed. When compared to Group C, the incidence of cough in Group D was significantly lower, and similarly, the severity of cough was also significantly different (p < 0.05, Table 2).

### Discussion

In our study, IV pretreatment with 10 mg of dexamethasone prior to the injection of the target concentration of remifentanil; 5 ng/ml; reduced the incidence of RIC from 26.5% to 6.5% (P < 0.05). In addition, in the group pretreated with 10 mg of dexamethasone, only mild or moderate levels of cough were noted, thereby significantly reducing the severity of cough when compared to Group C (p < 0.05).

In comparison with fentanyl, the starting time for remifentanil after induction of general anesthesia is fast and regardless of the injection time of each -opioid agonists, their half-lives are short (approximately 3–5 minutes), and they rapidly reach steady state. If remifentanil is injected continuously in the induction of general anesthesia, reduced doses of propofol may be used.

This could prevent the rapid decrease of blood pressure induced by propofol, avoid the rapid increase in blood pressure after response to stress such as tracheal intubation, therefore vital signs of patients could be more stable while inducing of general anesthesia [9].

It has been shown that cough develops in response to the administration of opioids, but the exact mechanisms have not been elucidated. However, opioid agents block the central sympathetic nervous system, activate the parasympathetic nervous system, and thus induce cough and the reflex contraction of the bronchus.

Reports that the administration of bronchodilators suppressed FIC support this possibility [4,5]. In addition, as another possible mechanism, the chemical reflex of the respiratory system mediated by fast acting irritant receptors located adjacent to the blood vessels in the respiratory system or vagal C-fibers receptors is also possible explanation [9]. Further, it has been also reported that opioids contract tracheal smooth muscles resulting in the irritation of the stimulatory receptor in the mucosa of the upper respiratory tract [10,11].

Kim et al. [1] have reported that to prevent RIC, a target remifentanil concentration of 4 ng/ml must be injected using a target infusion concentration device. When 0.5 mg/kg of

### Table 1. Patients’ Characteristics and Total Remifentanil Dose

|                      | Group C (n = 68) | Group D (n = 62) |
|----------------------|-----------------|-----------------|
| Sex (M/F)            | 25/43           | 36/26           |
| ASA physical status (I/II) | 58/10          | 54/8            |
| Age (yr)             | 41.1 ± 14.3     | 39.9 ± 14.3     |
| Height (cm)          | 163.9 ± 8.9     | 164.6 ± 9.8     |
| Weight (kg)          | 60.8 ± 9.8      | 63.8 ± 11.5     |
| Total remifentanil dose (μg) | 81.3 ± 14.4 | 84.7 ± 14.7 |

Values are mean ± SD or number of patients. Group C: pretreated with saline followed by remifentanil infusion at a target effect site concentration of 5 ng/ml, Group D: pretreated with 10 mg of dexamethasone followed by remifentanil infusion at a target effect site concentration of 5 ng/ml. Total remifentanil dose: Amount of infused remifentanil used until target effect site concentration of 5 ng/ml. There was no significant difference in any parameter between the groups.

### Table 2. The Incidence and Severity of Cough

| Group                  | Incidence | Severity of cough |
|------------------------|-----------|-------------------|
|                        |           | Mild (38.9%)      | Moderate (38.9%) | Severe (22.2%) |
| Control (n = 68)       | 18/68 (26.5%) | 7/18 (38.9%)     | 7/18 (38.9%)     | 4/18 (22.2%)  |
| Dexamethasone (n = 62) | 4/62 (6.5%)* | 2/4 (50%)*       | 2/4 (50%)*       | 0 (0%)*       |

The values are shown as the number of patients (%). Control group: pretreated with saline followed by remifentanil infusion at a target effect site concentration of 5 ng/ml, Dexamethasone group: pretreated with 10 mg of dexamethasone and remifentanil infusion at a target effect site concentration of 5 ng/ml, Severity of cough: mild (1–2), moderate (3–4), and severe (5 or greater). *P < 0.05 compared with saline group.
A limitation of our study was that 10 mg of dexamethasone was administered. In our study, 10 mg of dexamethasone was administered. The prevention of nausea and vomiting prior to surgery was not reported. Henzi et al. [22] have reported that in healthy patients, adverse effects of the injection of 8-10 mg of dexamethasone once for the prevention of nausea and vomiting prior to surgery was not proven. The dose of dexamethasone frequently used to prevent nausea and vomiting associated with surgery is 5-10 mg for adults. In our study, 10 mg of dexamethasone was administered. A limitation of our study was that 10 mg of dexamethasone was administered regardless of the weight of patient, and thus studies on a more exact dose (i.e. based on mg/kg) of individual patients are required.

In conclusion, pretreatment with 10 mg of dexamethasone prior to the injection of remifentanil suppressed the development and severity of cough induced by remifentanil without significant adverse effects.

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