Effect-Site Concentration of Remifentanil to Prevent Cough After Laryngomicrosurgery

Chul Ho Chang, MD, PhD; Jong Wha Lee, MD, PhD; Jong Rim Choi, MD; Yon Hee Shim, MD, PhD

Objectives/Hypothesis: The aim of this study was to discover the optimal effect-site concentration of remifentanil for cough prevention that does not delay awakening or cause respiratory depression during emergence from anesthesia with propofol and remifentanil in laryngomicrosurgery patients.

Study Design: Prospective, randomized, controlled trial.

Methods: One hundred five patients were randomly assigned to maintain an effect-site concentration (Ce) of remifentanil at a predetermined value of 1 (R1), 1.5 (R1.5), and 2 (R2) ng/mL during emergence. The incidence and grade (0, no coughing; 1, single cough; 2, more than one episode of nonsustained coughing; 3, sustained and repetitive coughing with head lift) of cough, emergence time, blood pressure (MAP), heart rate (HR), spontaneous respiratory rate, oxygen saturation, and postoperative nausea and vomiting (PONV) were recorded during emergence and recovery.

Results: The total number of patients with coughing during emergence was lower in groups R1.5 and R2 than in group R1. The cough grade during tracheal extubation was lower in groups R1.5 and R2 than in group R1. In group R2, emergence time was longer and postanesthesia care unit score was lower than in groups R1 and R1.5. Also in group R2, transient hypventilation and PONV were more frequent compared to group R1. There were no differences in MAP and HR among the three groups during emergence and recovery.

Conclusions: Maintenance of remifentanil at Ce 1.5 and 2 ng/mL suppressed coughing without serious adverse events during emergence from anesthesia with propofol and remifentanil in patients undergoing laryngomicrosurgery.

Key Words: Cough, emergence, extubation, remifentanil.

Level of Evidence: 1b

INTRODUCTION

Cough is a concern in the perioperative period. Cough during emergence from anesthesia is caused by stimulation from the endotracheal tube, anesthetic gas, or secretions and is not influenced by smoking history or β-adrenergic agonists.1 Cough results in bleeding in the surgical field and elevation of arterial, intracranial, and intraocular pressure. However, cough during emergence may be helpful in removing bronchial secretions. In vocal cord surgery, cough during emergence can result in vocal cord injury that could have deleterious effects on professional voice users, and stimuli to the vocal cord by the procedure itself can provoke coughing. Therefore, cough suppression during emergence is an important issue in laryngomicrosurgery.

Opioid infusion during emergence decreases coughing, agitation, and cardiovascular stimulation, but may lead to respiratory depression and delayed emergence.2 Remifentanil can be infused during emergence due to its short, context-sensitive half time and easy controllability. Low-dose remifentanil infusion during emergence from isoflurane anesthesia reduces not only coughing,3 but also hemodynamic changes in patients undergoing endoscopic sinus surgery. However, the optimal dose of remifentanil can be variable according to the characteristics of surgery and anesthesia. Total intravenous anesthesia (TIVA) is superior to balanced anesthesia with sevoflurane in suppressing cough and hemodynamic response.4–6 The aim of this study was to discover the effect-site concentration (Ce) of remifentanil that prevents cough during emergence from anesthesia with propofol and remifentanil in patients undergoing laryngomicrosurgery.

MATERIALS AND METHODS

Informed consent was obtained from all participants in the study, which was approved by our institutional review board (3–2009-0062). In total, 110 consecutive patients (ASA I–II); aged 20 to 65 years; scheduled for elective laryngomicrosurgery due to Reinke’s edema, laryngeal papilloma, vocal cord polyp, sulcus vocalis, or vocal cord cyst were included in this study. Five patients were dropped due to changes in the surgical plan. Patients with a history of chronic cough, asthma, recent respiratory tract infection, predicted difficult intubation,
Tracheostomy status, or significant cardiopulmonary, renal, or hepatic disease were excluded from the study.

The patients were premedicated with intravenous glycopyrrolate 0.1 mg in the preoperative preparation room. Electrocardiography, pulse oximetry, and a noninvasive blood pressure monitor were applied. End-tidal concentration of carbon dioxide was continuously monitored with a precalibrated S/5 Compact Anesthesia Monitor (Datex Omeda, Helsinki, Finland) at a sampling flow rate of 250 mL/min. A commercial target-controlled infusion (TCI) pump (Orchestra Base Primea, Fresenius Vial, France) was used for TCI of remifentanil and propofol according to Minto’s and Marsh’s pharmacokinetic models, respectively. TCI of remifentanil at 3 ng/mL and propofol 3 μg/mL was set for anesthetic induction. Rocuronium 0.6 mg/kg was administered after confirming unresponsiveness to eyelid reflex, and tracheal intubation was performed 120 seconds after rocuronium injection with a 6.0-mm cuffed endotracheal tube. End-tidal carbon dioxide concentration was maintained at 35 to 40 mmHg via controlled ventilation. Anesthesia was maintained with TCI of propofol at 2.5 to 4.0 mg/mL and remifentanil at 2.5 to 4.0 ng/mL to maintain blood pressure and heart rate. The same phonosurgeon performed all surgical procedures by LASER. Ketorolac 1 mg/kg and ondansetron 4 mg were administered intravenously at the end of surgery to prevent postoperative pain, nausea, and vomiting.

After completing the surgery, the propofol infusion was stopped, and remifentanil was adjusted according to group assignment by an anesthesiologist. Patients were randomly assigned to one of three groups (R1, R1.5, or R2) by a sealed envelope method. Target Ce of remifentanil was 1 ng/mL, 1.5 ng/mL, and 2 ng/mL in group R1, R1.5, and R2, respectively. After remifentanil Ce reached a predetermined value and neuromuscular recovery was confirmed by train-of-four stimuli, neostigmine 1 mg and glycopyrrolate 0.2 mg were administered intravenously. When patients spontaneously opened their eyes or responded to verbal commands, deep breathing was encouraged, and tracheal extubation was performed. The incidence and grade of coughing, Ramsay score, oxygen saturation, mean arterial pressure (MAP), heart rate (HR), spontaneous respiration rate (RR), and propofol Ce were recorded during emergence and recovery by another anesthesiologist who was blinded to the group assignment. The grade of coughing (grade 0, no cough; grade 1, light or single cough; grade 2, moderate cough or more than one episode of nonsustained coughing; grade 3, sustained and repetitive cough movements with head lift) was recorded at presence of endotracheal tube, during tracheal extubation, and 5 minutes after extubation. Grades 2 and 3 were considered severe cough. Ramsay score was assessed as 1, patient anxious and agitated, restless, or both; 2, patient cooperative, oriented, and tranquil; 3, patient responds to commands only; 4, patient exhibits brisk response to light glabellar tap or loud auditory stimulus; 5, patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus; 6, patient exhibits no response. Emergence time was defined as the time from propofol cessation to extubation. After confirmation of patient’s vital signs as stable, the patient was transferred to the postanesthesia care unit (PACU). Any episodes of bronchospasm, laryngospasm, desaturation (SpO2 <90%) or hypoventilation (spontaneous RR <8/min) during emergence were also recorded.

PACU score as activity, respiration, consciousness, circulation and oxygenation, postoperative nausea and vomiting (PONV), verbal numerical rating scales (VNRS) score for pain were recorded at PACU. Fentanyl 1 μg/kg was given when pain scores exceeded 5 by VNRS or patient requested analgesics. The recovery phase was defined as the time spent in the PACU.

### RESULTS

A total of 105 patients completed the study. Patient demographic data and operative characteristics were similar among all three groups (Table I). Also, propofol Ce doses were similar at 0.9 μg/mL among the three groups at tracheal extubation.

During emergence, the incidences of total and severe cough were significantly lower in groups R1.5 and R2 than group R1 (Table II). The cough grade in the presence of tracheal tube and during tracheal extubation were lower in groups R1.5 and R2 than group R1 (Fig. 1).

Emergence time was prolonged in group R2 compared to groups R1 and R1.5 (Table II). In group R2, the incidence of hypoventilation was more frequent than in group R1 at the presence of tracheal tube but not 5 minutes after extubation (Table II). There were no differences in MAP or HR among the three groups during emergence and recovery (Fig. 2).

Although activity, respiration, circulation, and oxygen saturation of PACU score were similar among groups, consciousness score was lower in group R2 than group R1. There were no differences in PACU stay, but incidence of PONV was higher in group R2 than group R1 (Table III).

### DISCUSSION

This study demonstrated that maintaining the Ce of remifentanil at 1.5 ng/mL and 2 ng/mL compared to
1 ng/mL during emergence reduced the incidence and severity of coughing in patients undergoing laryngomicrosurgery with propofol and remifentanil. Remifentanil Ce of 2 ng/mL delayed emergence and increased the incidence of hypoventilation and PONV, whereas remifentanil Ce of 1.5 ng/mL did not.

Cough reflex is known to be induced by central nervous system stimulation by stretch receptor under tracheal epithelial cell via vagus nerve. Topical application of lidocaine, deep extubation, and micro-opioid agonists suppress coughing by blocking tracheal epithelium stimulation. Coughing during emergence from general anesthesia for laryngomicrosurgery may cause complications such as bleeding and wound dehiscence. Removal of the endotracheal tube while the patient is still in a deep plane of general anesthesia, administration of local anesthetics to the trachea, or via intravenous route, and systemic narcotics may decrease the incidence and severity of coughing. However, deep extubation may pose the risk of desaturation with an unsecured airway and airway contamination by patient aspiration. When opioids, such as remifentanil, are constantly infused with the discontinuation of hypnotic agents, patient consciousness might be fully recovered without coughing. TIVA is associated with significantly less coughing and reduced hemodynamic response when compared with balanced anesthesia of inhalation anesthetics.

<table>
<thead>
<tr>
<th>Table II. Data on Cough During Emergence.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients with cough</td>
</tr>
<tr>
<td>Total number of patients with severe cough</td>
</tr>
<tr>
<td>Emergence time, min</td>
</tr>
<tr>
<td>Hypoventilation</td>
</tr>
<tr>
<td>In the presence of tracheal tube</td>
</tr>
<tr>
<td>Five minutes after tracheal extubation</td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation or number (%). Group R1, R1.5, or R2: remifentanil Ce was maintained during emergence at 1, 1.5, or 2 ng/mL, respectively.

†P < .05 compared to group R1.
§P < .05 compared to group R1.5.
Ce = effect-site concentration.
during emergence from general anesthesia. It might result from intrinsic cough prevention effect by propofol and remifentanil. TCI might prevent excess or insufficient doses of remifentanil.

In this study, remifentanil Ce at 1.5 ng/mL and 2 ng/mL reduced coughing caused by the endotracheal tube compared to Ce of 1 ng/mL. A recent study in thyroid surgery patients showed that EC95 of remifentanil to reduce coughing at emergence from propofol-remifentanil anesthesia was 2.14 ng/mL analyzed by Dixon’s up-and-down method. The incidence of total cough at 2 ng/mL of remifentanil Ce was as high as 46% in this study. The higher incidence of cough in this study might be due to direct surgical stimulation of vocal cord surgery. The incidence of severe cough at 1.5 ng/mL remifentanil in this study was 6%, although another study in thyroid surgery showed 0% severe cough with 1.5 ng/mL remifentanil. Another reason for the differences may be due to different definitions and grading systems. Although Lee et al. evaluated the presence of cough (which was defined as a strong and sudden contraction of the abdomen), we graded the severity of cough. In our study, the incidence of severe cough at 2 ng/mL remifentanil Ce was zero.

Cough during emergence was altered by anesthetic agents. For example, coughing was induced more in general anesthesia with desflurane than with sevoflurane. Total intravenous anesthesia is associated with significantly less coughing and reduced hemodynamic response when compared with balanced anesthesia with inhalation anesthetics. The risk of coughing after spine surgery is lower after propofol anesthesia compared with sevoflurane anesthesia. This could be due to the intrinsic cough prevention effect of propofol.

Spontaneous respiratory rate in the presence of a tracheal tube was lower in remifentanil Ce of 2 ng/mL than 1 ng/mL and 1.5 ng/mL. Spontaneous respiratory rates during tracheal extubation and 5 minutes after tracheal extubation at remifentanil Ce 2 ng/mL were similar to those at 1 ng/mL and 1.5 ng/mL. Higher doses of the remifentanil infusion might attenuate respiratory drive and elicit hypoventilation. Patients with remifentanil infusion at Ce 2 ng/mL had delayed awakening and low score of consciousness in the PACU and high incidence of PONV compared to remifentanil Ce at 1 ng/mL and 1.5 ng/mL. However, remifentanil Ce at 1.5 ng/mL suppressed coughing similar to Ce 2 ng/mL without those adverse events. Therefore, remifentanil Ce 2 ng/mL use during short operations may require additional monitoring and support of respiratory function, as well as preventive medication for PONV.

The TCI system delivers IV drugs to constantly maintain Ce according to the drug’s pharmacokinetic behavior using an infusion pump controlled by a computer. Based on a three-compartment model (central, rapidly equilibrating, and slowly equilibrating)

| TABLE III. Recovery Profile in the PACU. |
| Group R1, n = 35 | Group R1.5, n = 35 | Group R2, n = 35 |
| PACU stay, min | 39 ± 6 | 40 ± 10 | 44 ± 13 |
| PACU score at admission | 10 ± 10 | 10 ± 10 | 8 ± 1 |
| PONV | 2 (6%) | 7 (20%) | 12 (34%) |
| Pain (VNRS) | 1 (0–2) | 1 (0–2) | 1 (0–2) |

Values are mean ± standard deviation or number (%) or median (interquartile range), R1, R1.5, or R2: remifentanil Ce was maintained during emergence at 1, 1.5, or 2 ng/mL, respectively.

P < .05 compared to group R1.

PACU = postanesthesia care unit; PONV = postoperative nausea and vomiting; VNRS = verbal numerical rating scale.
compartments), the computer calculates the infusion rate that is necessary to achieve a user-designated Ce. The computer directs the infusion pump to administer the appropriate dosage of a drug after calculating the infusion rate, as the drug accumulates in the patient’s body. The computer frequently recalculates the appropriate dosage based on the computer’s pharmacokinetic simulation of the Ce. Administration of drugs via TCI is a reliable technique for reaching a defined target concentration without concern for an increase in drug level beyond the intended range.

There were a few limitations in this study. First, Ce of remifentanil and propofol was calculated by pharmacokinetic modeling irrespective of pharmacodynamic variability, instead of using a measured value. Second, tracheal stimulation by an endotracheal tube and laryngoscope was similar in all patients, but the intensity of surgical stimuli was not equivalent due to operation and operative time.

CONCLUSION
Remifentanil TCI at Ce 1.5 and 2 ng/mL during emergence from anesthesia with propofol and remifentanil prevents cough in patients after laryngomicrosurgery. However, at remifentanil Ce 2 ng/mL, the risk of delayed awakening, hypoventilation and PONV may increase, which warrants special attention.

BIBLIOGRAPHY