Sex differences in remifentanil requirements for preventing cough during anesthetic emergence

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ABSTRACT

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Purpose: Target-controlled infusion (TCI) of remifentanil can suppress coughing during emergence from general anesthesia, but previous studies under different clinical conditions have recommended significantly different effective effect-site concentrations (effective Ce) of remifentanil for 50% of patients (EC_{50}). The differences among these studies include type of surgery and patient sex. In recent years, there has been a growing interest in studying sex differences in anesthetic pharmacology. Therefore, we determined the effective Ce of remifentanil for each sex under the same clinical conditions.

Materials and Methods: Twenty female and twenty-five male ASA I–II grade patients between the ages of 20 and 46 who were undergoing thyroidectomy were enrolled in this study. The effective Ce of remifentanil for preventing cough was determined for each sex using the isotonic regression method with a bootstrapping approach following Dixon's up-and-down method.

Results: Isotonic regression with a bootstrapping approach showed that the estimated EC_{50} of remifentanil for preventing coughing during emergence was significantly lower in females [1.30 ng/ml (83% confidence interval, 1.20–1.47 ng/ml)] than in males [2.57 ng/ml (83% CI, 2.45–2.70 ng/ml)]. Mean EC_{50} in females was also significantly lower than in males (1.23 ± 0.21 ng/ml vs. 2.43 ± 0.21 ng/ml, $P<0.001$). MAP, HR and RR over time were not significantly different between the sexes.

Conclusion: When using remifentanil TCI for cough prevention during anesthetic emergence, patient sex should be a considered for appropriate dosing.

Key words: sex difference; effect-site concentration; general anesthesia; remifentanil; target-controlled infusion; cough prevention

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I. INTRODUCTION

Airway reflexes, including coughing, are commonly seen normal responses during emergence from general anesthesia [1–3]. However, coughing during emergence may lead to a number of potentially dangerous side effects, including laryngospasm, detrimental hemodynamic changes, and increased intraocular and intracranial pressure. In particular, post-thyroidectomy bleeding resulting in acute airway obstruction or re-operation occurs in 1–4 %

of patients [4–7], and severe cough may cause such bleeding [4, 7]. In addition to surgeon-related factors, anesthetic factors may also assist in prevention of the post-thyroidectomy bleeding. A smooth extubation without significant coughing or retching to avoid raised venous or arterial pressures are important considerations in minimizing the risks of postoperative hemorrhage [7]. During awakening from endotracheal anesthesia, the trachea may be stimulated by the endotracheal tube, by noxious effects of the anesthetic gas itself, or by uncleared secretions [3]. The presence of an endotracheal tube during emergence from general anesthesia is often associated with severe cough [3, 8]. Therefore, prevention of cough during emergence from general anesthesia with the presence of a tracheal tube may be important in patients undergoing certain operations.

Intravenous opioids delivered at the end of surgery can facilitate smooth emergence by reducing coughing [9, 10] and attenuate deleterious hemodynamic changes [11]. Specifically, administration of remifentanil via a target-controlled infusion (TCI) makes it possible to reach a defined target concentration without the concern that remifentanil levels will rapidly decrease or increase beyond the intended range [12]. Previous studies have shown reduction of airway reflexes during emergence by using remifentanil TCI,[13, 14] but the recommended effect-site concentrations (Ce) of remifentanil (EC_{50}) range

from 1.46 ng/ml to 2.35 ng/ml [13, 14]. The differences between these studies include type of surgery, combined anesthetics, and patient sex.

Numerous animal and human studies suggest that sex may affect opioid analgesia; that is, males require higher doses of opioids to achieve similar levels of analgesia as females [15–17]. This sex difference is known to occur mainly with mu- and kappa- receptor agonists. Sex differences in appropriate opioid dose may affect not only the analgesic system but also act on other inherent properties of the endogenous opioid receptor system, such as respiratory function [18]. Mu- and kappa- opioid receptors in the brainstem contribute to regulation of the cough reflex [19]. If there is significant sex difference in remifentanil concentration for airway suppression during anesthetic emergence, some dose regimen which is suitable for one sex could be excessive for the other sex; so, this information would be clinically important not only in respect of effect but also preventing complications.

Based on the information above, we hypothesized that men may require higher concentrations of remifentanil for cough suppression during anesthetic emergence than women. The purpose of this study was to determine the EC_{50} of remifentanil in effect-site TCI for preventing cough in males and females under the same clinical conditions and evaluate whether there are sex differences in EC_{50} of remifentanil for emergence cough suppression.

II. MATERIALS AND METHODS

1. Patient Selection

This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (Ref: 4-2011-0356) and registered at http://ClinicalTrials.gov (Ref: NCT01614535). Written informed consent was obtained from all subjects. We enrolled 30 male and 23 female patients, ages 20 to 46 and ASA I–II, who underwent general anesthesia for elective thyroidectomy. Exclusion criteria included patients who had signs of a difficult airway, upper respiratory infection in the previous two weeks, hypertension, or Diabetes Mellitus (DM). Current smokers were excluded, and female patients who were pregnant, breast-feeding or menopausal were also excluded. In addition, we withdrew patients who had delayed emergence and had not regained consciousness by 15 min after the main anesthetic agent had been stopped.

2. Study Design

The patients were not premedicated. After arrival at the operating room, routine

monitoring, including electrocardiogram, peripheral oxygen saturation, non-invasive arterial pressure, end-tidal carbon dioxide ($EtCO_2$), and nasopharyngeal temperature were performed. Bispectral index (BIS) (BIS® monitor, Covidien Medical, Boulder, CO) monitoring was also performed. Anesthesia was induced using propofol 1.5–2.5 mg/kg intravenously (I.V.) and remifentanil TCI. For TCI of remifentanil, a commercial TCI pump (Orchestra® Base Primea, Fresenius Vial, France) was used, and pump operation was based on the pharmacokinetic model of Minto et al [20]. After non-response to verbal orders and loss of eyelid reflex, rocuronium 0.6 mg/kg I.V. was administered. Tracheal intubation was performed in all patients using a 6.5 mm (internal diameter) tracheal tube for females and a 7.5 mm tracheal tube for males. Cuff pressure was maintained at 20–25 cmH_2O using a hand pressure gauge (Hi-Lo™ Hand Pressure Gauge, VBM Medizintechnik GmbH, Germany). Anesthesia was maintained with sevoflurane at 1.5–2.5 vol% in an air/oxygen mixture (FIO_2: 0.5, 2 l/min) to achieve BIS values of 40-55, and the remifentanil Ce of 2–5 ng/ml was used to maintain patients' mean arterial pressure (MAP) and heart rate (HR) within 20% of baseline values. Mechanical ventilation was maintained with a tidal volume of 8 ml/kg, and ventilator frequency was adjusted to maintain $EtCO_2$ at 35–40 mmHg. Nasopharyngeal temperature was maintained at 36–37℃.

Three anesthetists carried out this study. The first conducted anesthetic induction, maintenance, and control of remifentanil concentration during the emergence period. The second, who did not know the remifentanil concentration during emergence, was the lead during anesthetic emergence and extubation. The third anesthetist recorded all variables of interest to this study, including cough grading, and was blinded to the Ce of remifentanil. Ten min before the end of surgery, sevoflurane was adjusted to an approximate BIS level of 60, and the remifentanil Ce was titrated to a pre-determined concentration (the initial Ce of remifentanil being 2 ng/ml). This "predetermined Ce" was maintained for at least 15 min throughout emergence. When the operation was completed, 30 mg of ketorolac and 4 mg of ondansetron were given, and 0.004 mg/kg of glycopyrrolate and 0.02 mg/kg of neostigmine were given intravenously to reverse neuromuscular block. Simultaneously, sevoflurane was discontinued, and fresh gas flow was increased to 10 l/min. Mechanical ventilation was converted to manual ventilation 3 min after sevoflurane discontinuation, and $EtCO_2$ was maintained at 45–55 mmHg. During this phase, the patients were not disturbed except with a verbal request to open their eyes. When the patients opened their eyes, deep breathing was encouraged. The tracheal tube was pulled out when spontaneous respiration with an adequate tidal volume was

confirmed. Immediately after extubation, remifentanil infusion was stopped, and oxygen was supplemented via a facemask for at least 10 min.

Emergence cough was defined as the cough occurring from the time sevoflurane was turned off to 5 min after extubation. The level of cough was assessed and recorded by the following cough grading system (Grade 0, no cough; Grade 1, single cough with mild severity; Grade 2, cough persistence less than 5 s with moderate severity; Grade 3, severe, persistent cough for more than 5 s). For estimation of the effective remifentanil Ce, the up-and-down sequential allocation design was used [21]; that is, the predetermined Ce of remifentanil was determined according to the cough response of the previous patient. If the patient did not cough throughout the peri-extubation period, the pre-determined concentration of remifentanil for the subsequent patient was decreased by 0.4 ng/ml. Similarly, if the patient coughed anytime around extubation, the pre-determined concentration was increased by 0.4 ng/ml. The upper concentration was limited to 3.0 ng/ml due to concern for patient safety after extubation [8, 14]. The stopping rule, which required at least six pairs of failure/success, necessitated the recruitment of more than 20 patients [22]. This up-and-down method was conducted independently for each sex.

The MAP and HR were recorded at the following time points: T1, before

induction of anesthesia (baseline); T2, end of surgery; T3, before extubation; T4, just after extubation; T5, 5 min after extubation; T6, 10 min after extubation; T7, before transfer out from the postanesthetic care unit (PACU). If MAP < 60 mmHg or HR < 50 beats per min (beats/min), we injected ephedrine 4 mg I.V. or atropine 0.5 mg I.V. immediately. In addition, respiratory rate (RR) was recorded at the T4–7 points. The time to eye opening (sevoflurane off to eye opening) and time to extubation (sevoflurane off to extubation) were also recorded. Bradypnea, which was defined as a RR < 8 breaths per min (bpm), and SpO_2 below 95% despite oxygen supplementation were monitored during the entire emergence period.

3. Statistical Analysis

Patient data are presented as mean ± standard deviation (SD), or median and range, or numbers of patients. According to previous studies in which the EC_{50} was estimated by the Dixon's method [13], the stopping rule required at least six pairs of failure/success. The EC_{50} of remifentanil was defined as the mean value of the independent crossover pairs for each sex, and we compared the mean EC_{50}s using a t-test. To specify the precision of the target concentration, the isotonic regression method was also used for estimating

EC_{50} and EC_{95} along with a confidence interval (CI) [23]. From an observed response rate, which is the ratio of the number of successful patients to the number of subjects at each concentration level, an adjusted response probability was calculated by pooled adjacent-violators algorithm (PAVA) in order to adhere to the assumption in dose-response determinations that drug effect increases with increased dosage. The CI was estimated by a boot strapping approach [22, 24]. If the value of EC_{50} does not overlap at the level of 83% CI, the null hypothesis of equal concentration can be rejected with a type I error of 0.05 [25]. Other normally distributed variables were analyzed using t-tests. Chi-square tests were used for intergroup comparisons of ordinal variables. Statistical analyses were performed using SAS (version 9.2, SAS Inc., Cary, NC, U.S.), and a P value of less than 0.05 was considered significant.

III. RESULTS

23 female and 30 male patients were enrolled in the study. Among the enrolled patients, three female patients were excluded due to surgical factors (nerve injury and delayed skin suture) and an incorrect pre-determined concentration

of remifentanil. Five male patients were excluded due to surgical factors (converted from simple thyroidectomy to modified radical neck dissection) and delayed emergence. The patients' characteristics are presented in Table 1. Age was comparable between the females and males; however, due to sex differences, patients' height, weight, body surface area (BSA), and body mass index (BMI) were significantly lower in females. Also, the number of patients for each cough grade was comparable between the females and males.

The up-and-down results in consecutive patients are seen in Fig. 1. The EC_{50} of remifentanil needed to prevent cough during emergence based on Dixon's method was significantly less in females (1.23 ± 0.21 ng/ml) than in males (2.43 ± 0.21 ng/ml) ($P<0.001$).

TABLE 1. Patient characteristics

	Male group (n=25)	Female group (n=20)	P value
Age	38.36 ± 4.40	37.25 ± 6.81	0.53
Height	173.20 ± 4.22*	161.12 ± 5.61	< 0.001
Weight	75.62 ± 11.46*	56.30 ± 5.84	< 0.001
BMI	25.22 ± 3.80*	21.76 ± 2.70	0.0013
BSA	1.90 ± 0.148*	1.59 ± 0.09	< 0.001
ASA classification			0.62
1	22 (88%)	18 (95%)	
2	3 (12%)	1 (5%)	
Sevoflurane vol% at BIS60	1.08 ± 0.21	1.06 ± 0.16	0.76

Values are presented as mean ± SD or number (percentage). BMI indicates body mass index; BSA, body surface area.

*P<0.05 between groups.

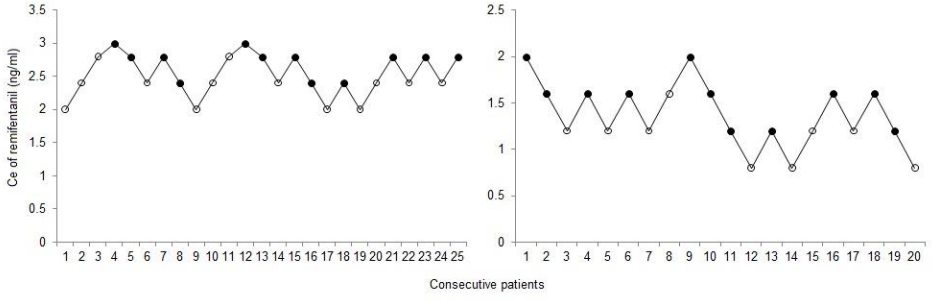

FIGURE 1. Assessment of success or failure of smooth emergence over the predetermined concentration of remifentanil based on consecutive patients by Dixon's up-and-down method. Mean EC_{50} for smooth emergence was calculated from cross-over pairs from failure (open circle) to success (closed circle) from 25 male patients (left) and 20 female patients (right). EC_{50} indicates the effect-site concentration of remifentanil for suppression of emergence cough in 50% of patients.

The use of isotonic regression estimator, with CIs derived by a bootstrapping approach, revealed that the EC_{50} of remifentanil was significantly lower in females than in males: 1.30 ng/ml (83% CI, 1.20–1.47 ng/ml) vs. 2.57 ng/ml (83% CI, 2.45–2.70 ng/ml). Similarly, the EC_{95} was significantly lower in females than in males: 1.86 ng/ml (95% CI, 1.56–1.96 ng/ml) vs. 2.96 ng/ml (95% CI, 2.77–2.98 ng/ml) (Table 2). PAVA response rates of both sexes are presented in Fig. 2.

TABLE 2. EC_{50} and EC_{95} of remifentanil for emergence without cough

	M	F
Isotonic regression(EC_{50}, 83% CI) †	2.57(2.45-2.70)	1.30(1.20-1.47)
Isotonic regression(EC_{95}, 95% CI) ‡	2.96(2.77-2.98)	1.86(1.56-1.96)

Values are presented as the mean (83%† or 95%‡ CI). EC_{50} and EC_{95}were calculated by isotonic regression method using the PAVA, and CIs were calculated using a bootstrapping approach. EC_{50} indicates the Ce of remifentanil required to suppress emergence cough in 50% of patients; EC_{95}, the Ce of remifentanil required to suppress emergence cough in 95% of patients; PAVA, Pooled-adjacent-violators algorithm; CI, confidence interval.

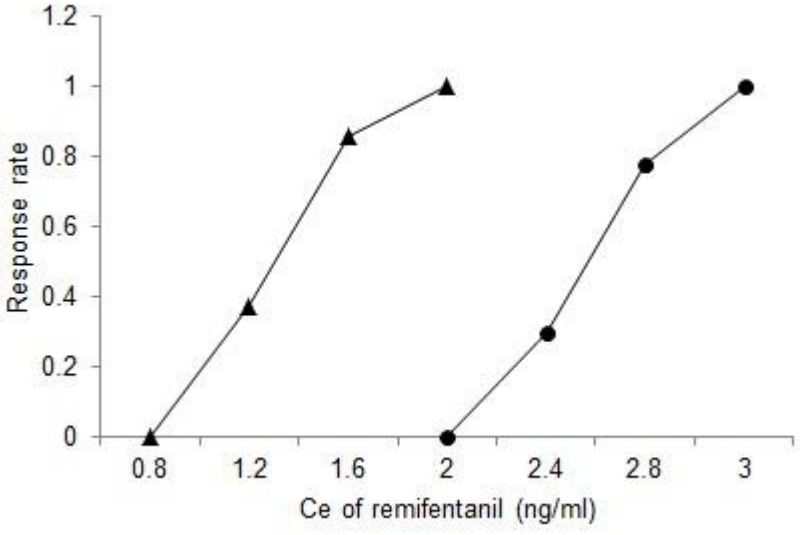

FIGURE 2. Pooled-adjacent-violators algorithm response rate in female (▲) and male (●) groups. EC_{50} of remifentanil in females was 1.30 ng/ml (83% CI, 1.20–1.47 ng/ml) and in males was 2.57 ng/ml (83% CI, 2.45–2.70 ng/ml). EC_{95} in females was 1.86 ng/ml (95% CI, 1.56–1.96 ng/ml) and in males was 2.96 ng/ml (95% CI, 2.77–2.98 ng/ml). Both EC_{50} and EC_{95} were significantly lower in the female group than in the male group. EC_{50} indicates the effect-site concentration of remifentanil for suppressing emergence cough in 50% of patients; EC_{95}, the effect-site concentration of remifentanil for suppressing emergence cough in 95% of patients; CI, confidence interval.

RR was 6.2, 9.1, 11.2, and 13.8 bpm at the T4–7 points, respectively, and RR at T5 and T6 points was significantly faster in females, though there was no difference of RR pattern between sexes over time (p-value of sex*time = 0.28) (Fig. 3). In females, bradypnea, defined as a RR < 8 bpm, was observed just after extubation (T4 point) in two of seven patients with a Ce of 1.6 ng/ml. In males, bradypnea was observed in two of ten patients with a Ce of 2.4 ng/ml, in one of nine patients with a Ce of 2.8 ng/ml, and in one of two patients with a Ce of 3.0 ng/ml. One male patient with a Ce of 2.8 ng/ml developed upper airway obstruction and experienced a brief desaturation episode. All of these patients who had adverse respiratory events returned to a normal respiratory pattern within 5 min by encouragement of deep breathing via facial mask without ventilatory support.

The time to eye opening was significantly faster in females (6.50 ± 1.64 min) than in males (10.01 ± 4.43 min) (P<0.001). The time to extubation was also significantly faster in females (7.66 ± 1.91 min) than in males (11.27 ± 4.95 min) (P<0.001) (Table 3).

MAP and HR over time did not differ significantly between the sexes [p-value of sex*time = 0.35 (MAP) and 0.08 (HR)] (Fig. 3). The MAP of females was significantly lower than that of males at the T2, 6 and 7 points (p=0.01, p<0.001, and p<0.001). HR did not differ between sexes at any time point.

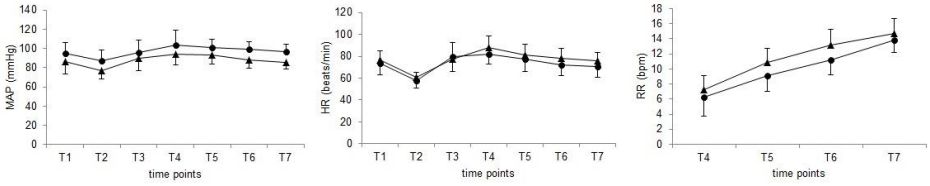

FIGURE 3. MAP, HR and RR were not significantly different in female (▲) and male (●) over time (p-value of sex*time for MAP, HR, and RR = 0.35, 0.08 and 0.28, respectively). MAP, HR and RR over time did not differ significantly between the sexes. RR increased continuously from each prior time point in both males and females: just after extubation to 5 min after extubation ($p<0.001$), 5 min after extubation to 10 min after extubation ($p<0.001$), and 10 min after extubation to before transfer out from the post-anesthetic care unit ($p<0.001$). MAP indicates mean arterial pressure; HR, heart rate; RR, respiratory rate; bpm, breaths per min.

TABLE 3. The time to eye opening and the time to extubation in males and females

	Male group (n=25)	Female group (n=20)	P value
Time to eye opening (min)	10.01 ± 4.43	6.50 ± 1.64	< 0.001
Time to extubation (min)	11.27 ± 4.95	7.66 ± 1.91	0.0021

Values are presented as mean ± SD. The time to eye opening was defined as the time from sevoflurane discontinuation to eye opening. The time to extubation was defined as the time from sevoflurane discontinuation to extubation. SD indicates standard deviation.

IV. DISCUSSION

In the present study, we found that the remifentanil requirement for cough suppression during anesthetic emergence in 50% patients was 1.30 ng/ml in females, which was about half of the concentration in males, 2.57 ng/ml.

Several studies have investigated the effective Ce of remifentanil for preventing airway reflexes during anesthetic emergence. Jun et al. demonstrated that 1.5 ng/ml of remifentanil effectively suppressed cough during emergence from sevoflurane-remifentanil anesthesia for thyroid surgery [26]. However, Chen et al. reported that 2–2.5 ng/ml was needed to achieve the antitussive effect of remifentanil following propofol anesthesia for nasal surgery [8]. The most notable difference between the two studies is type of surgery; in addition, the proportion of male patients in the former study was 14%, whereas it was 62% in the latter. It is not surprising that the opioid requirements differed by sex, but other confounding factors should be excluded. Therefore, we conducted the present study for sex comparison only. Based on our results, the concentrations required for cough suppression during anesthetic emergence under the same clinical conditions are significantly different between sexes. One interesting point is that the cough sensitivity of females was lower than that of males. Dicpinigaitis and Rauf

reported that healthy women have a more sensitive cough reflex than healthy men [27]. Nevertheless, the antitussive effect was achieved at a lower concentration of remifentanil in females than in males. Male patients with a Ce of 2.0 ng/ml will definitely suffer from severe cough during emergence, while female patients with the same Ce will almost never cough.

Recently, there has been growing interest in studying sex differences in anesthetic pharmacology. Compared to males, females are less sensitive to the anesthetic effects of propofol [28, 29] and ropivacaine [30], but are more sensitive to vecuronium [31, 32] and rocuronium [33]. Of the anesthetic drugs, morphine is the most commonly studied with regard to sex differences, and several studies have shown that females are more sensitive to the analgesic effects of morphine than are males [34, 35]. Sex differences related to opioids are not restricted to analgesic properties, but are also present in other opioid–mediated responses, including the respiratory system. For instance, morphine has greater effect on decreasing ventilatory response to carbon dioxide and hypoxic sensitivity in females than in males [18]. Most of these studies did not measure morphine or morphine glucuronide concentration, so pharmokinetic differences could not be excluded, but the major difference is thought to be pharmacodynamic [17].

Remifentanil TCI is derived from the results of pharmacokinetic and

pharmacodynamic studies, which demonstrate that there are no sex differences related to pharmacokinetic or electroencephalogram (EEG) variables [20]. However, there is a lack of studies about the differential effect of remifentanil based on sex [36], and the clinical effects of opioids may differ from EEG variables. Experimental studies for mu-opioid receptor binding, measured by PET, demonstrated that premenopausal females have significantly higher mu-receptor binding potentials than males in the cortical and sub-cortical areas [37]. Similarly, Zubieta et al. found that tonic experimental pain produced a greater decrease in mu-opioid receptor availability in several brain regions among men when compared to women, apparently due to increased pain-induced binding of endogenous ligand to the receptor [38]. Therefore, the authors suggested that the higher mu-opioid receptor availability among females might explain their increased analgesic responses to exogenous opioids. This pharmacodynamic difference can also be expected in remifentanil, and our results did demonstrate a sex difference related to cough suppression.

Several clinical studies reported respiratory complications at concentrations over 2.5 ng/ml (Ce of remifentanil) [8, 14], and our result did as well. Though the respiratory complications were not severe and resolved spontaneously or with minimal treatment, further studies regarding the safety of the suggested

EC_{95} are necessary for generalized application of high concentrations of remifentanil.

There are some limitations in the present study. First, we did not measure plasma concentrations of remifentanil. Rather, we calculated the predicted value using Minto's pharmacokinetic model, which is widely used in clinical settings with acceptable levels of bias and inaccuracy [39]. Second, the types of surgery included were limited. Thyroid surgery may involve more tracheal irritation than other surgeries, therefore caution is needed in extending the findings of this study to other types of surgery.

V. CONCLUSION

In conclusion, when remifentanil TCI is used for cough prevention during anesthetic emergence, patient sex may be an important factor for the determination of optimal remifentanil concentrations. Overall, females require lower concentrations of remifentanil for this purpose than do males.

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ABSTRACT (IN KOREAN)

마취회복 중 발생하는 기침을 적절히 억제하기 위한 레미펜타닐 효과처 농도의 성별간 차이

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레미펜타닐의 효과처 농도 목표 주입은 마취에서의 회복 시 기관내관 발관 전후로 발생하는 기침을 효과적으로 억제하는 것으로 알려져 있다. 그러나 여러 다른 임상적 상황에서 수행한 연구마다 보고한 EC_{50}, 즉 50% 환자의 기침을 억제하기에 적절한 레미펜타닐의 효과처 농도가 큰 차이를 보였다. 이 연구간의 차이점은 수술의 종류와 환자의 성별이 포함된다. 최근 마취 약리학에서 성별의 차이에 대한 관심이 증가하고 있는데, 보고된 EC_{50}간의 차이도 성별에 기인한 것일 가능성이 있다. 본 연구는 같은 임상적 상황에서 마취 회복 시 기침 억제를 위해 레미펜타닐의 효과처 농도 목표 주입을 사용할 때, 각각의 성별에서 적절한 기침 억제를 할 수 있는 레미펜타닐의 효과처 농도를 구하여 그 차이를 비교하고자 한다.

본 연구는 만 20~46세의 미국 마취과학회 신체등급 1~2등급의 성인 중 전신마취 하에 갑상전 절제술을 받는 20명의 여성과 25명의 남성을 대상으로 하였다. 50%와 95% 환자에서 마취 회복 시 기관내관 발관 전후 기침을 억제하기에 적절한 레미펜타닐의 효과처 농도, 즉 EC_{50}와 EC_{95}는 Dixon's up-and-down 방법, isotonic regression 방법과 bootstrapping approach 를 사용하여 구하였다.

Isotonic regression 방법과 bootstrapping approach으로 계산한 EC_{50}은 남자[2.57 ng/ml (83% confidence interval (CI), 2.45-2.70 ng/ml)] 에 비해 여자[1.30 ng/ml (83% CI, 1.20-1.47 ng/ml)] 에서 통계학적으로 유의하게 낮았다. Dixon's up-and-down 방법으로 구한 평균 EC_{50}도 여자가 남자에 비해 통계학적으로 유의하게 낮았다 (1.23 ± 0.21 ng/ml vs. 2.43 ± 0.21 ng/ml, $P<0.001$). 시간의 흐름에 따른 평균 동맥압, 맥박수, 호흡수의 변화 양상은 성별 간에 유의한 차이를 보이지 않았다.

결론적으로 마취 회복 시 기관내관 발관 전후 기침을 억제하기 위한 목적으로 레미펜타닐의 효과처 농도 목표 주입을 사용한다면, 환자의 성별을 고려하여 적절한 농도를 결정해야 한다.

핵심되는 말: 성별 간의 차이, 효과처 농도 목표 주입, 전신 마취, 레미펜타닐, 기침 억제