Comparison of the Incidence and Severity of Cough after Alfentanil and Remifentanil Injection

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－ABSTRACT －

Comparison of the Incidence and Severity of Cough after Alfentanil and Remifentanil Injection

Introduction: Intravenous administration of fentanyl derivatives can induce cough paradoxically. This study examined the incidence and severity of cough after a bolus of alfentanil and remifentanil.

Methods: Four-hundred sixty five patients, aged 18-70 years, were allocated randomly to three groups to receive alfentanil 10 μg/kg, remifentanil 1 μg/kg, or an equal volume of 0.9% saline intravenously over 10 s. Any episode of cough was classified as coughing and graded as mild (1-2), moderate (3-4) or severe (5 or more).

Results: The overall incidence of cough was higher in the opioid groups than the saline group. The remifentanil group [39/150 patients; 26.0%, (95% CI, 19.6-33.6%)] showed a higher incidence than the alfentanil group [11/152 patients; 7.2%, (95% CI, 0.4-12.6%)] ($P < 0.001$). There was no significant difference in the severity of cough between alfentanil and remifentanil group.

Conclusion: This study demonstrated that the equipotent boluses of alfentanil and remifentanil induced coughing, even though the incidence of cough after alfentanil administration was lower than that after remifentanil administration.

Key words : Alfentanil, remifentanil, opioid induced cough

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ABBREVIATIONS

ASA : American Society of Anesthesiologists

SpO_2 : Oxygen Saturation of arterial Pulsations

SD : Standard Deviation

CI : Confidence Interval

MAP : Mean Arterial blood Pressure

HR : Heart Rate

NMDA : N-methyl-D-aspartate

I. INTRODUCTION

Fentanyl and its derivatives, which are selective μ-opioid receptor agonists, are mainly used for pain management. However, one of their interesting effects during anesthesia induction is the attenuation of the hemodynamic and respiratory responses. One of the undesirable effects of respiratory response is also laryngeal morbidity.

Although blunting of cough is one of the useful effects of opioids during tracheal intubation, intravenous administration of fentanyl derivatives can induce cough paradoxically (Agarwal, et al., 2007; Bohrer, et al., 1990; Horng, et al., 2007; Kim, et al., 2008; Phua, et al., 1991).

Cough during the induction of general anesthesia may be explosive, sometimes requiring immediate intervention when it is associated with undesirable increases in the intracranial, intra-ocular, and intra-abdominal pressures (Ambesh, et al., 2009; Tweed, et al., 2001; Yemen, 1998).

According to previous reports, the incidence of fentanyl-induced cough varies from 28 to 65% (Agarwal, et al., 2003; Bohrer, et al., 1990; Horng, et al., 2007; Lin, et al., 2004; Pandey, et al., 2004; Phua, et al., 1991), and the incidence of cough after remifentanil and sufentanil administration was reported to be 27% and 15%, respectively (Agarwal, et al., 2007; Kim, et al., 2008).

Alfentanil is one of the fentanyl derivatives with a rapid onset of effect similar to that of remifentanil (Egan, 1995). However, there are no reports of the incidence and severity of cough after alfentanil administration.

This study examined the incidence and severity of cough associated with an intravenous bolus of alfentanil and remifentanil.

II. PATIENTS AND METHODS

This study was approved by the institutional review board and written informed consent was obtained from all patients. Four-hundred sixty five patients, ASA physical status I or II, aged 18-65 years, undergoing general anesthesia for elective surgery, were enrolled in this study.

The exclusion criteria included body mass index exceeding 30 kg/m^2, a history of bronchial asthma or chronic obstructive pulmonary disease, respiratory tract infection, and hypertension treated with angiotensin converting enzyme inhibitors.

No premedication was administered prior to surgery. Before arrival in the operating theater, a 20-gauge cannula was inserted into the forearm or dorsum of the hand, and connected to a T-connector for drug injection. Upon arrival in the operating theater, all patients were monitored with electrocardiogram, pulse oximeter, noninvasive blood pressure and capnography. The patients were assigned randomly to three groups using computer generated random numbers.

No other drugs were given to the patients in the operating theater before the study drugs. Immediately after injection, an observer, blinded to the drug therapy, recorded the occurrence of cough as 'yes' or 'no', over 1 min period, and the onset time (from the start of infusion to the beginning of coughing).

Depending upon the number of coughs observed, the cough severity was graded as mild (1–2), moderate (3–5) and severe (> 5). The patients received either intravenous alfentanil 10 μg/kg (diluted with normal saline to make 0.2 mg/ml), remifentanil 1 μg/kg

(diluted with normal saline to make 0.02 mg/ml) or equal volume of 0.9% saline administered over 10 seconds.

Each drug was administered at a constant rate over 10 seconds using a commercial infusion pump (Orchestra®, Fresenius Vial, France). Induction of anesthesia was commenced only after any coughing had subsided. Assisted mask ventilation with oxygen was applied if desaturation was observed (SpO_2 < 90%). The incidence of apnea and truncal rigidity after study drug injection was also recorded.

Considering that the incidence of remifentanil-induced cough in earlier studies was 27% (Kim, et al., 2008), and assuming a 50% decrease in the incidence of cough after alfentanil, this study required at least 149 patients per group to achieve a 5% level of significance and 80% power of test. The sample size was increased to 155 patients per group to take into account any dropouts.

Statistical analyses were performed using the statistical package (SPSS 13.0 for windows, SPSS Inc, Chicago, IL, USA). Data is reported as the mean ± standard deviation (SD) or number of patients. Patients' characteristics, the difference in onset time to cough and hemodynamic variables between the groups were compared using one way ANOVA with Bonferroni correction. Incidence and severity of cough were analyzed using a chi-square test. A P value < 0.05 was considered significant. Logistic regression was used to establish the association between patient's variables and alfentanil or remifentanil-induced cough and results were presented in odds ratio (OR) and 95% confidence interval (CI) of OR was also calculated.

III. RESULTS

Nine patients did not complete the study due to technical problems, such as IV line obstruction and disconnection (3 in the alfentanil group, 5 in the remifentanil group and 1 in the saline group). There were no significant differences in the patient characteristics between the three groups (Table 1).

Table 1. Patients' characteristics

	Saline (n = 154)	Alfentanil (n = 152)	Remifentanil (n = 150)
Sex (M/F)	81/73	83/69	67/83
Age (years)	42.3 ± 14.2	38.8 ± 13.7	40.3 ± 12.4
Weight (kg)	63.1 ± 10.7	64.0 ± 10.5	63.4 ± 11.4
Height (cm)	165.4 ± 9.0	165.9 ± 9.2	164.0 ± 8.0
Smoker	35 (22.7%)	40 (26.3%)	33 (22.0%)
ASA physical status, I/II	128/26	116/36	121/29

Values are mean ± SD or numbers. No significant differences were noted between the groups.

The incidence of cough was higher in the opioid groups than in the saline group, with remifentanil group [39/150 patients; 26.0% (95% CI, 19.6-33.6%)] showing a higher incidence than alfentanil group [11/152 patients; 7.2% (95% CI, 0.4-12.6%)] ($P < 0.001$). However, there was no significant difference in the severity of cough between alfentanil and remifentanil groups (Table 2). In the alfentanil group, 11 patients had cough, with 7, 3 and 1 of those patients experiencing mild, moderate and severe cough, respectively. This was similar to the remifentanil group, in which 27, 9 and 3 out of 39 patients who coughed showed mild, moderate and severe cough, respectively.

Table 2. Incidence of cough and its severity after alfentanil, remifentanil or saline infusion.

Group	No cough	Incidence and severity of cough				Onset (s)
		Total	Mild	Moderate	Severe	
Saline (n = 154)	154	0	0	0	0	0
Alfentanil (n = 152)	141*	11 (7.2%)*	7 (63.6%)	3 (27.3%)	1(9.1%)	26.4 ± 4.7
Remifentanil (n = 150)	111	39 (26.0%)	27 (69.2%)	9 (23.1%)	3 (7.7%)	24.7 ± 4.4

Values are numbers or mean ± SD.

*$P < 0.001$ compared with remifentanil group.

Onset times of cough were 26.4 ± 4.7 seconds after alfentanil infusion and 24.7 ± 4.4 seconds after remifentanil infusion (Table 2). It ranged from 18 to 35 seconds after alfentanil or remifentanil infusion (Fig. 1).

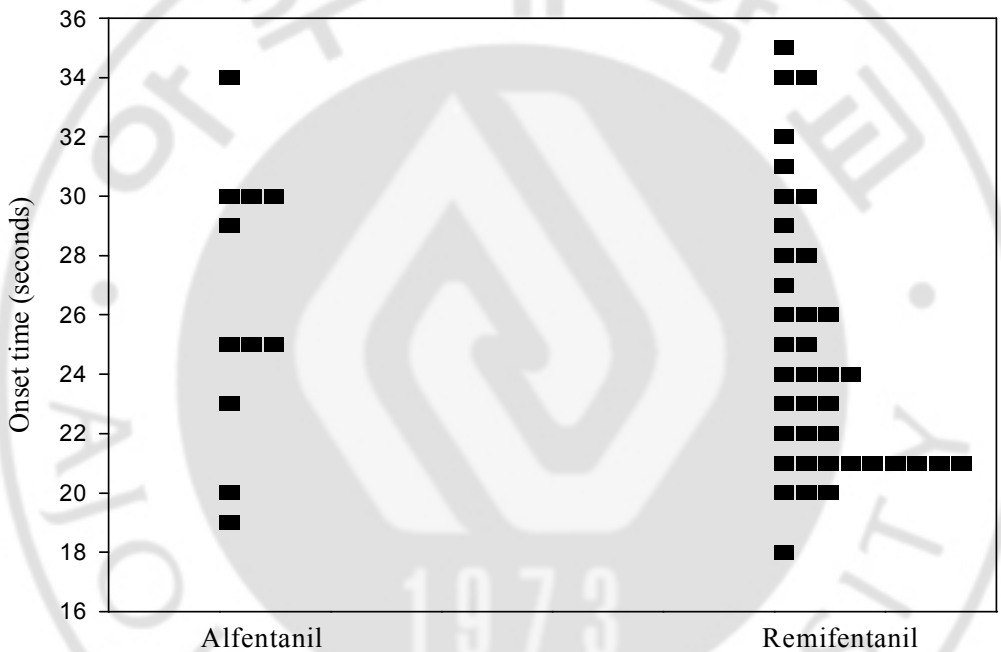

Fig. 1 Distribution of onset times of cough after alfentanil or remifentanil infusion.

The demographic characteristics of the patients with or without cough are listed in Table 3. In the remifentanil group, the percentage of smokers was greater in the patients without cough than in the patients with cough.

Table 3. Demographic characteristics with or without cough induced by alfentanil or remifentanil.

	Alfentanil (n=152)		Remifentanil (n=150)	
	Cough (n=11)	No cough (n=141)	Cough (n=39)	No cough (n=111)
Age (years)	34.8 ± 16.6	39.1 ± 13.5	41.4 ± 13.3	39.9 ± 12.1
Sex (M:F)	7 : 4	76 : 65	21 : 18	46 : 65
Smoker	2 (18.2%)	38 (27.0%)	4 (10.3%)	29 (26.1%)*

Values are numbers or mean ± SD.

*$P < 0.05$ compared with patients with cough within the group.

The results of logistic regression between patients' variables and alfentanil or remifentanil induced cough are listed in Table 4. In the remifentanil group, male gender was associated with increased remifentanil-induced cough [OR (95% CI) = 2.70 (1.20 – 6.05)], and smoking was associated with reduced remifentanil-induced cough [OR (95% CI)] = 0.20 (0.06 – 0.66)], but not in the alfentanil group.

Table 4. Effect of Demographic characteristics on cough induced by alfentanil or remifentanil.

	Alfentanil (n=152)		Remifentanil (n=150)	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age	0.98 (0.93 - 1.03)	0.38	1.00 (0.97 – 1.03)	0.93
Sex (male)	1.65 (0.42 – 6.57)	0.48	2.70 (1.20 – 6.05)	0.02
Smoking	0.46 (0.87 – 2.42)	0.36	0.20 (0.06 – 0.66)	0.008

OR : odds ratio, CI : confidence interval.

Table 5 lists mean arterial blood pressure (MAP), heart rate (HR) and oxygen saturation of arterial pulses (SpO_2) during anesthesia induction. Compared with the baseline values, MAP decreased significantly 1 min after infusion in the alfentanil and remifentanil groups, and HR increased significantly 1min after infusion in the remifentanil group. However, MAP and HR in both groups were within normal limits, and no intervention was required. MAP, HR, and SpO_2 at 1 min after infusion were similar in the three groups. None of the patients suffered from hypoxemia, desaturation, apnea, truncal rigidity, or other adverse effects.

Table 5. Mean arterial pressure and heart rate during anesthesia induction.

	Group	Baseline	1 min after infusion
MAP (mmHg)	Saline	94.1 ± 12.9	93.9 ± 12.4
	Alfentanil	95.2 ± 13.9	92.7 ± 13.7*
	Remifentanil	97.1 ± 14.5	93.6 ± 14.4*
HR (beats/min)	Saline	70.7 ± 13.1	70.4 ± 13.4
	Alfentanil	71.5 ± 12.8	72.4 ± 13.7
	Remifentanil	72.1 ±13.4	74.1 ± 15.8*
SpO2 (%)	Saline	98.3 ± 1.4	98.4 ± 1.5
	Alfentanil	98.7 ± 1.3	98.4 ± 2.3
	Remifentanil	98.6 ± 1.5	98.4 ± 2.1

Values are mean ± SD.

*$P < 0.05$ compared with baseline value.

MAP, mean arterial blood pressure; HR, heart rate.

IV. DISCUSSION

The main finding of this study is that intravenous alfentanil 10 μg/kg provoked coughing in 7.2% of patients when injected over 10 seconds, and this incidence was lower than with remifentanil-induced cough (27% of patients).

The incidence of cough after remifentanil 1 μg/kg administered over 10 seconds in this study was similar to that in a previous study on remifentanil-induced cough (27 vs. 27.6%, respectively) (Kim, et al., 2008). In the previous study, remifentanil was administered at a target effect-site concentration of 4 ng/ml using target controlled infusion system, in which a bolus dose of approximately 1 μg/kg was administered over 10 seconds.

This study revealed a relatively lower incidence of cough with alfentanil (7.2%) compared with other fentanyl derivatives, such as fentanyl (28-65%) (Agarwal, et al., 2003; Bohrer, et al., 1990; Horng, et al., 2007; Lin, et al., 2004; Pandey, et al., 2004; Phua, et al., 1991), remifentanil (27.6%) (Kim, et al., 2008) and sufentanil (15.8%) (Agarwal, et al., 2007).

The precise mechanism for the tussive effect of opioids is still unclear. Some studies reported that fentanyl inhibits central sympathetic outflow, thereby activating the vagus nerve, which induces cough and reflex bronchoconstriction (Agarwal, et al., 2003; Lui, et al., 1996; Reitan, et al., 1978). Lui et al. hypothesized that fentanyl-induced cough is due to bronchoconstriction. They evaluated the effects of nebulized terbutaline (β_2 agonist) and concluded that terbutaline inhalation effectively suppressed the cough response from 43% to 3% (Lui, et al., 1996).

Another likely mechanism is pulmonary chemoreflex, which is mediated by either irritant-receptors (rapidly adapting receptors) or by vagal C fibers receptors in proximity to pulmonary vessels (juxta-capillary receptors) (Bohrer, et al., 1990; Paintal, 1969).

The frequency of alfentanil and remifentanil-induced cough in this study may depend on the injection speed and the concentration of the injectate. Lin et al. reported that fentanyl provoked cough in 18% of patients when injected within 2 seconds but the incidence of cough decreased to 1.3% when the injection time was increased to 30 seconds (Lin, et al., 2005). In addition, Yu et al. reported a decrease in the occurrence of coughing after diluting fentanyl with 0.9% saline with near elimination of fentanyl-induced cough (2%) using diluted fentanyl injected over 30 seconds (Yu, et al., 2007).

The early occurrence of cough in this study (< 30 seconds) may be due to rapid onset of action of remifentanil and alfentanil. The onset time of cough after fentanyl injection is reported to 42 seconds after 5 μg/kg bolus over 5 seconds and 9 seconds after 7 μg/kg bolus over 1 second (Bohrer, et al., 1990; Lui, et al., 1996). In addition to pharmacokinetic properties of opioids, dosage and injection time may be the contributing factors on the onset of cough.

Kim et al. reported that remifentanil-induced coughs were of short duration and self-limiting (Kim, et al., 2010). In their study, coughing occurred early, sometimes within 5 seconds of initiating the infusion, but had stopped after 1 minute similar to our results (Table 2, Figure 1). During this period, plasma concentrations increase up to a peak level, maintaining at higher than effect-site concentration, while actual effect-site concentrations are low, but slowly increasing. They speculated that the tussive effect of remifentanil could

be from a peripheral mechanism, with cough occurring when the plasma concentration is high and effect-site concentration is low. This speculation could explain some phenomena including paradoxical tussive and antitussive effects of opioids, and the different incidence rates of cough according to the injection rates of opioids. Before the injected opioids reach the effect-site where the opioids act as antitussives, rapidly increased opioids in plasma may show tussive effects via pulmonary receptors.

Young age may be the risk factor for opioid-induced cough (Kim, et al., 2008; Oshima, et al., 2006). This could be explained by a decrease in the number of rapidly adapting stretch receptors with aging in dogs(Pontoppidan, et al., 1960). However, age was not risk factor for alfentanil or remifentanil-induced cough in our study (Table 4).

Chronic tobacco exposure augments substance P-evoked increase in activity of the rapidly adapting receptors and the irritant receptor and thus induces airway hyperresponsiveness (Bonham, et al., 1996; Joad, et al., 1996). Smoking cessation clearly improves airway hyperresponsiveness(Willemse, et al., 2004), which is closely related to cough(Chang, et al., 1997; Hsiue, et al., 1993). However, there are some reports that smokers have decreased cough sensitivity (Kim, et al., 2008; Oshima, et al., 2006), supporting the hypothesis that nicotine inhibits or blocks C-fiber activity in the sensory nervous system of the lower respiratory tract (Lin, et al., 2005; Millqvist, et al., 2001). In our study, non-smoker was an independent risk factor for remifentanil-induced cough (Table 4), which is consistent with the previous study on remifentanil-induced cough by Kim et al.(Kim, et al., 2008).

We observed increased probability of remifentanil-induced cough in male gender (Table 4), although other studies reported that no gender difference was found (Kim, et al.,

2008; Oshima, et al., 2006). We think that large-scale study is needed to find the gender difference in opioid-induced cough.

The mechanism for the higher incidence of cough after remifentanil administration in this study is not known. Because clinical preparations of alfentanil and remifentanil are available as hydrochloride salts without citrate salts, the amount of citrate cannot be the possible explanation of the cough, as in sufentanil and fentanyl (Agarwal, et al., 2007). One plausible explanation is the presence of glycine in the clinical preparation of remifentanil. Each vial of Ultiva® (GlaxoSmithKline, Verona, Italy) contains 1, 2, or 5 mg of remifentanil base; 15 mg glycine; and hydrochloric acid to buffer the solutions. In an experimental study with guinea-pigs, direct administration of 1 μg glycine into the cough center potentiated a cough response, as indicated by an increase in the amplitude of respiration curves of cough caused by mechanical stimulation of the mucosa of the tracheal bifurcation (Honda, et al., 1990). Another explanation is the difference in the stimulation of N-methyl-D-aspartate (NMDA) receptors. The presence of NMDA receptors has been demonstrated in the larynx, lung and airways (Robertson, et al., 1998), and these receptors were suggested to be involved in regulating the cough reflex (Kamei, et al., 1989). Experimental studies have demonstrated that remifentanil activates NMDA receptors (Guntz, et al., 2005; Hahnenkamp, et al., 2004). This NMDA receptor activation by remifentanil might explain the relatively high incidence of remifentanil-induced cough.

In conclusion, 10 μg/kg alfentanil injection induced cough in 7.2% of patients when injected over 10 seconds, and the incidence of cough after alfentanil administration was lower than that after remifentanil administration when 1 μg/kg remifentanil was injected over

same period.

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– 국문요약 –

Alfentanil 과 remifentanil 정주 후 나타나는 기침의 발생 빈도와 정도 비교

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조 한 범

(지도교수 : 이 숙 영)

연구 배경: 기침억제작용은 fentanyl 을 비롯한 아편유사제의 유용한 작용임에도 불구하고 마취유도 전 기관내삽관에 의한 혈역학적 부작용을 경감시키기 위하여 투여한 아편유사제가 많은 환자에서 기침을 유발시킨다고 알려져 있다. 본 연구에서는 alfentanil 과 remifentanil 일회 부하용량 주입 시 나타나는 기침의 발생 빈도 및 정도를 비교하였다.

대상 및 방법: 18 세에서 70 세의 465 명의 환자를 대상으로 하여 무작위로 세 그룹으로 나누어 alfentanil 10ug/kg, remifentanil 1ug/kg, 또는 동량의 0.9% 생리식염수를 10 초에 걸쳐 주입하였다. 이후 나타나는 기침의 횟수를 기준으로 기침의 정도를 경도(1-2 회), 중등도(3-4 회), 고도(5 회 이상)로 나누어 기록하였다.

결과: 전반적인 기침의 발생 빈도는 생리 식염수 그룹에 비해 아편유사제 그룹이 높았다. remifentanil 그룹 (26.0%)은 alfentanil 그룹(7.2%)에 비해 유의하게 기침 발생 빈도가 높았다. 기침의 정도는 alfentanil 그룹과 remifentanil 그룹 간에 유의한 차이는 없었다.

결론: 이번 연구를 통하여 대등한 용량의 alfentanil 과 remifentanil 일회 부하용량 주입 시 기침 발생 빈도는 alfentanil 이 remifentanil 에 비해 낮게 나타나나 두 약제 모두 기침을 유발 할 수 있다는 것을 알 수 있다.

핵심어 : Alfentanil, Remifentanil, 아편 유사제에 의한 기침