Clinical Research Article

Korean J Anesthesiol 2014 September 67(3): 171-174
http://dx.doi.org/10.4097/kjae.2014.67.3.171

The effect of injection speed on remifentanil-induced cough in children

Dae-Hee Kim, Ji-Young Yoo, Bong-Ki Moon, Baek-Hyun Yoon, and Jong-Yeop Kim

Department of Anesthesiology and Pain Medicine, Ajou University School of Medicine, Suwon, Korea

Background: Remifentanil sometimes elicits cough during induction of anesthesia, as with the use of other fentanyl congeners. We designed this study to investigate the incidence of remifentanil-induced cough (RIC) in children and to evaluate the effect of injection speed on RIC.

Methods: One hundred twenty ASA physical status I–II patients, aged 3–12 yr, undergoing general anesthesia were enrolled in the study. Patients were randomly assigned to one of the three groups. Patients in Group R30 received remifentanil 1.5 μg/kg at a constant rate over 30 s. Patients in Group R45 received remifentanil 1.5 μg/kg over 45 s, and patients in Group R60 received remifentanil 1.5 μg/kg over 60 s, respectively. Episodes of cough were recorded and graded as mild (1–2), moderate (3–4), or severe (5 or more). Mean arterial pressure (MAP), heart rate (HR), and SpO_2 were recorded on arrival in the operating room (baseline) and 1 min after remifentanil infusion.

Results: The incidence of RIC was 33.3% in Group R30 (13 of 39 patients), 17.9% in Group R45 (7 of 39 patients), and 5.0% in Group R60 (2 of 40 patients). Patients in Group R60 had a significantly lower incidence of RIC than those in Group R30 ($P = 0.001$). The MAP, HR, and SpO_2 values were not significantly different between groups.

Conclusions: When intravenous remifentanil 1.5 μg/kg was administered in pediatric patients, the incidence of RIC decreased from 33 to 5% by increasing the injection time from 30 to 60 s. Remifentanil should be administered slowly over 60 s in children to suppress cough during anesthesia induction. (Korean J Anesthesiol 2014; 67: 171-174)

Key Words: Anesthesia, Cough, Injection speed, Remifentanil.

Received: January 15, 2014. Revised: February 14, 2014. Accepted: March 20, 2014.

Corresponding author: Jong-Yeop Kim, M.D., Department of Anesthesiology and Pain Medicine, Ajou University School of Medicine, 206, World cup-ro, Yeongtong-gu, Suwon 443-749, Korea. Tel: 82-31-219-5574, Fax: 82-31-219-5579, E-mail: kjyeop@ajou.ac.kr

Introduction

Remifentanil, a synthetic opioid used as an analgesic and antitussive agent, sometimes causes cough during induction of anesthesia, as with the use of other fentanyl congeners, such as fentanyl, alfentanil, and sufentanil [1-4]. The incidence of cough after intravenous administration of remifentanil varies between 26 and 54% [1,3-6]. Although opioid-induced cough is usually benign and self-limiting in most patients; it may be explosive, especially in children. Some authors have reported that severe fentanyl-induced cough (FIC) can cause multiple conjunctival and periorbital petechiae [7], and explosive, spasmodic coughing leads to massive engorgement of tongue and hypopharynx that can cause acute airway obstruction and severe hypoxia [8]; both these occurrences were reported in the pediatric population. In addition, since FIC is more common in children, occurring even after the administration of small doses and a more severe episode can develop after the administration of larger doses [9,10]; prevention of opioid-induced cough is particularly important in children. Meanwhile, prolongation of the injection time is a simple and safe method to effectively suppress FIC [11,12]. To date, there are no studies evaluating the frequency of remifentanil-induced cough (RIC) and the effect of injection speed on RIC in children. Therefore this study was designed to investigate the incidence of RIC in children and to evaluate the effect of injection speed on RIC.

Materials and Methods

This study was approved by the Institutional Review Board and parents of all patients provided written informed consent. One hundred twenty ASA physical status I–II, un-premedicated, patients, aged 3–12 years, undergoing general anesthesia were included in this study. Patients with weight exceeding 20% of the ideal body weight, a history of bronchial asthma, respiratory tract infection were excluded. A 24-gauge cannula was placed over the dorsum of the hand, or forearm and connected to a T-connector for drug injection before arrival in the operating room. A researcher, blind to patient allocation, prepared the study syringe for each patient. Upon arrival in the operating room, standard monitoring was applied with electrocardiogram, pulse oximeter, and noninvasive blood pressure.

Patients were randomly assigned to one of the three groups as a computer-generated, randomized manner. Patients in Group R30 received remifentanil 1.5 μg/kg (diluted with normal saline to make 10 μg/ml) at a constant rate over 30 s with a syringe pump (Orchestra®, Fresenius Vial, Brezins, France). Patients in Group R45 received remifentanil 1.5 μg/kg over 45 s, and patients in Group R60 received remifentanil 1.5 μg/kg over 60 s, respectively. All patients were preoxygenated with 100% oxygen over 1 min before remifentanil administration. After IV remifentanil infusion, the onset time (from the start of infusion pump to the beginning of coughing) and severity of cough were observed for 1 min and recorded by an observer who was blinded to the duration of injection given to the patients. Severity of coughing was graded based on the number of episodes of cough (mild, 1–2; moderate, 3–4; and severe, 5 or > 5) [9]. Assisted mask ventilation with oxygen was applied if desaturation was observed (SpO_2 < 95%). The incidence of apnea and muscle rigidity after remifentanil injection was also recorded. Apnea was defined as a pause in breathing that lasts more than 15 s by inspection, and muscle rigidity was defined as increased muscle tone, which renders facemask ventilation during induction difficult or impossible. Mean arterial pressure (MAP), heart rate (HR), and SpO_2 were recorded on arrival in the operating room (baseline) and 1 min after remifentanil infusion. Following the study was terminated, anesthesia was induced with propofol, and maintained using sevoflurane with oxygen and air.

The authors hypothesized that the incidence of cough during remifentanil administration would be reduced with slow injection of remifentanil. Therefore, the primary outcome was the reduction in the incidence of RIC and the secondary outcome was the severity of RIC.

Based on the reports demonstrating an incidence of RIC of 34% [6], and assuming that the incidence of RIC would be less than 5% after applying a regimen; this study required at least 38 subjects per group for 5% level of significance and 80% power of test with the correction for multiple comparisons. The sample size was increased to 40 patients per group assuming the occurrence of dropouts.

Statistical analyses were performed with the statistical package (SPSS 13.0 for windows, SPSS Inc, Chicago, IL, USA). Data are presented as mean ± SD or number of patients. Patient characteristics, differences in the onset time of RIC, and hemodynamic variables among the groups were compared using one-way ANOVA with the Bonferroni correction. Incidence and severity of RIC were analyzed using a Fisher's exact test or chi-square test. P value < 0.05 was considered statistically significant.

Results

Two patients did not complete the study protocol due to IV line obstruction and anxiety. There were no differences in patient characteristics between the groups, in terms of age, gender, weight, and ASA physical status (Table 1). The incidence and characteristics of RIC are shown in Table 2. Incidence of RIC was 33.3% (13/39 patients) in Group R30, 17.9% (7/39 patients) in Group R45, and 5.0% (2/40 patients) in Group R60. Patients in Group R60 had a significantly lower incidence of RIC than those in Group R30 (P = 0.001). However, there was no sig-

Table 1. Patient Characteristics

	Group R30 (n = 39)	Group R45 (n = 39)	Group R60 (n = 40)
Age (yr)	7.1 ± 1.9	6.7 ± 1.9	6.3 ± 2.2
Sex (M/F)	23/16	28/11	28/12
Weight (kg)	24.7 ± 6.2	24.4 ± 8.1	24.0 ± 7.2
ASA class (I/II)	35/4	34/5	37/3

Values represent mean ± SD or numbers. Group R30: remifentanil 1.5 μg/kg was injected over 30 s, Group R45: remifentanil 1.5 μg/kg was injected over 45 s, Group R60: remifentanil 1.5 μg/kg was injected over 60 s.

Table 2. Incidence and Characteristics of Remifentanil-induced Cough

	Group R30 (n = 39)	Group R45 (n = 39)	Group R60 (n = 40)
Incidence	13 (33.3%)	7 (17.9%)	2 (5.0%)*
Severity			
Mild (1–2)	6	3	1
Moderate (3–4)	4	2	1
Severe (> 5)	3	2	0
Onset (sec)	27.5 ± 4.6	26.3 ± 7.8	30.5 ± 2.1
Number of cough	3.3 ± 2.4	3.4 ± 2.6	3.0 ± 1.4
Duration of cough (sec)	4.5 ± 4.3	4.0 ± 3.3	2.0 ± 1.4

Values represent the number of patients (proportion) or mean ± SD. Group R30: remifentanil 1.5 μg/kg was injected over 30 s, Group R45: remifentanil 1.5 μg/kg was injected over 45 s, Group R60: remifentanil 1.5 μg/kg was injected over 60 s. *P < 0.05 compared with Group R30.

nificant difference in the incidence of RIC between Group R30 and Group R45. Also, there was no significant difference in the severity of RIC between the groups. None of the patients developed loss of consciousness and apnea during the study period. However, muscle rigidity occurred and SpO_2 decreased to 92% in one patient of the Group R30 after coughing, and mask-assisted ventilation with 100% oxygen was applied.

MAP, HR and SpO_2 values during anesthesia induction are listed in Table 3. The MAP, HR, and SpO_2 values at baseline and 1 min after remifentanil infusion were not significantly different between groups.

Discussion

This study demonstrated that intravenous remifentanil 1.5 μg/kg, when administered over a 30 s period, provoked cough in 33% of pediatric patients, and that the incidence of RIC decreased to 5%, when it was injected slowly over a 60 s period.

The incidence of RIC in the adults has been reported to be between 26 and 54% [1,3-6]. Shen et al. [4] found that the incidence of RIC was 54% in the adult patients (18–60 years) when 2 μg/kg remifentanil was injected over 5 s. In the study by Cho et al. [3], 26% of adult patients (18–70 years) developed a cough after receiving 1.0 μg/kg remifentanil over 10 s. In our study,

Table 3. Mean Arterial Pressure and Heart Rate during Anesthesia Induction

	Group	Baseline	1 min after remifentanil infusion
MAP (mmHg)	R30	81.5 ± 11.2	78.5 ± 11.0
	R45	80.1 ± 9.7	76.2 ± 12.5
	R60	80.0 ± 12.1	74.2 ± 12.9
HR (beats/min)	R30	95.9 ± 12.0	93.0 ± 12.9
	R45	91.8 ± 10.4	90.4 ± 13.2
	R60	95.4 ± 13.4	92.7 ± 14.0
SpO_2 (%)	R30	99.7 ± 0.6	99.6 ± 1.5
	R45	99.5 ± 0.6	99.6 ± 0.5
	R60	99.7 ± 0.6	99.4 ± 0.9

Values represent the mean ± SD. Group R30: remifentanil 1.5 μg/kg was injected over 30 s, Group R45: remifentanil 1.5 μg/kg was injected over 45 s, Group R60: remifentanil 1.5 μg/kg was injected over 60 s, MAP: mean arterial blood pressure, HR: heart rate.

when remifentanil 1.5 μg/kg (diluted to 10 μg/ml with 0.9% saline) was administered over 30 s, the incidence of cough was 33 % in children (3–12 years). On the other hand, the incidence of cough was less than 2% when fentanyl was administered over a 30 s period in previous studies [11,12]. Lin et al. [11] reported that the incidence of cough by fentanyl (100 or 150 μg) was 1.3% in patients, aged 18-80 years. And, Yu et al. [12] reported the incidence of cough by 3 μg/kg fentanyl (diluted to 10 μg/ml with 0.9% saline) was 2% in patients, aged 18–65 years. Taken together, remifentanil might provoke cough more commonly than fentanyl. Remifentanil might cause adverse effects such as muscle rigidity, or hemodynamic instability more commonly. It has been reported that 59% of patients experienced hypoxemia (< 90%) that required manually assisted mask ventilation, when remifentanil was administered by IV push over 5 s in the adult patients [4]. Therefore, in a routine clinical setting, remifentanil should be administered slowly and cautiously during anesthetic induction, especially in children.

It is recommended that remifentanil should be administered over at least 30 s, when given as a bolus infusion at induction [13]. Although remifentanil was injected over 30 s in this study, according to the recommendations, remifentanil provoked cough in 33% of the children. Incidence of RIC decreased to 18% when the injection time was increased to 45 s, and the incidence of RIC decreased to 5% when the injection time was increased to 60 s. These results imply that incidence of RIC seems to be inversely related to the injection time. From a pharmacologic viewpoint, remifentanil is likely to induce cough when the plasma concentration of remifentanil increases abruptly, and consequently, the plasma concentration of remifentanil is greater than the effect-site concentration of remifentanil. The duration of the drug infusion time can affect the peak plasma concentration. The peak plasma concentration is decreased as the infusion time is prolonged. If remifentanil is injected over 60 s, the possibility

of reaching the plasma concentration threshold for cough will be lesser because remifentanil has a brief half-time for equilibration between plasma and effect-site ($t_{1/2}k_{e0}$ of 1.0–1.5 min) [14]. Although the discrepancy between plasma and effect-site concentration of remifentanil existed, when remifentanil was injected over 30 s in this study, remifentanil did not provoke cough in 67% of children. Thus, the difference between the plasma concentration and the effect-site concentration of remifentanil or equilibrium state could not explain the mechanism of RIC entirely. Further studies are warranted to elucidate these issues.

Because the injection speed and doses of opioids are the important factors that affect the frequency of cough, the incidences of RIC in this pediatric study could not be directly compared to those in previous adult studies [1,3]. The incidence of RIC might be different between children and adults. Lin et al. [15] assumed that higher frequency of cough induced by fentanyl in children may be associated with heightened irritant receptor activity (rapidly adapting receptors), which mediate the pulmonary chemoreflex in the tracheal smooth muscle. Furthermore, it was found that the number of rapidly adapting receptors decreased with age in an animal study [16]. The study to investigate this issue might be needed.

In conclusion, the incidence of RIC was 33% in children when 1.5 μg/kg remifentanil was administered over a 30 s period, and prolonged administration of remifentanil over 60 s effectively suppressed RIC. Remifentanil should be administered slowly in children for safe and smooth induction, especially in case as the first drug of anesthetic sequence.

References

1. Kim JY, Park KS, Kim JS, Park SY, Kim JW. The effect of lidocaine on remifentanil-induced cough. Anaesthesia 2008; 63: 495-8.
2. Agarwal A, Gautam S, Nath SS, Gupta D, Singh U. Comparison of the incidence and severity of cough induced by sufentanil and fentanyl: a prospective, randomised, double-blind study. Anaesthesia 2007; 62: 1230-2.
3. Cho HB, Kwak HJ, Park SY, Kim JY. Comparison of the incidence and severity of cough after alfentanil and remifentanil injection. Acta Anaesthesiol Scand 2010; 54: 717-20.
4. Shen JC, Xu JG, Zhou ZQ, Liu HJ, Yang JJ. Effect of equivalent doses of fentanyl, sufentanil, and remifentanil on the incidence and severity of cough in patients undergoing abdominal surgery: A prospective, randomized, double-blind study. Cur Ther Res Clin Exp 2008; 69: 480-7.
5. Min SK, Kim DH, Cho HB, Moon BK, Kim JY. Limited maximal flow rate of target-controlled remifentanil infusion and induced cough. Anaesthesia 2012; 67: 145-8.
6. Lim JH, Ryu SJ, Lim YS. The incidence of cough induced by remifentanil during anesthetic induction was decreased by graded escalation of the remifentanil concentration. Korean J Anesthesiol 2010; 58: 117-21.
7. Tweed WA, Dakin D. Explosive coughing after bolus fentanyl injection. Anesth Analg 2001; 92: 1442-3.
8. Ambesh SP, Singh N, Srivastava K. Fentanyl induced coughing caused life-threatening airway obstruction in a patient with arteriovenous malformation of tongue and hypopharynx. Int J Anesthesiol 2009; 20: 7.
9. Han JI, Lee H, Kim CH, Lee GY. The frequency of fentanyl-induced cough in children and its effects on tracheal intubation. J Clin Anesth 2010; 22: 3-6.
10. Oshima T, Kasuya Y, Okumura Y, Murakami T, Dohi S. Identification of independent risk factors for fentanyl-induced cough. Can J Anaesth 2006; 53: 753-8.
11. Lin JA, Yeh CC, Lee MS, Wu CT, Lin SL, Wong CS. Prolonged injection time and light smoking decrease the incidence of fentanyl-induced cough. Anesth Analg 2005; 101: 670-4.
12. Yu H, Yang XY, Zhang X, Li Q, Zhu T, Wang Y, et al. The effect of dilution and prolonged injection time on fentanyl-induced coughing. Anaesthesia 2007; 62: 919-22.
13. Mallick A, Elliot S. Remifentanil is too potent to be given by bolus. Br J Anaesth 2004; 93: 305-6.
14. Glass PS, Gan TJ, Howell S. A review of the pharmacokinetics and pharmacodynamics of remifentanil. Anesth Analg 1999; 89(4 Suppl): S7-14.
15. Lin CS, Sun WZ, Chan WH, Lin CJ, Yeh HM, Mok MS. Intravenous lidocaine and ephedrine, but not propofol, suppress fentanyl-induced cough. Can J Anaesth 2004; 51: 654-9.
16. Pontoppidan H, Beecher HK. Progressive loss of protective reflexes in the airway with the advance of age. JAMA 1960; 174: 2209-13.