EC_{50} and EC_{95} of remifentanil to prevent rocuronium-induced withdrawal movements in children

Hye Jin Park, Hyoseok Kang, Eu-Gene Kim, Juyoun Choi, and Jeong Sung Seo

Department of Anesthesiology and Pain Medicine, Eulji Hospital, Eulji University College of Medicine, Seoul, Korea

Background: Intravenous administration of rocuronium induces intense pain in most patients (60−100%). This could be harmful during anesthesia induction because of the unintended reflex movement of an unconscious patient in response to the pain. Previous studies have reported that remifentanil effectively reduces rocuronium-induced pain and withdrawal movements. This study was designed to evaluate the EC_{50} and EC_{95} of remifentanil to prevent withdrawal movements in children.

Methods: We enrolled a total of 171 pediatric patients scheduled for general anesthesia in this study. Remifentanil was administered by target-controlled infusion. Effect-site target concentrations ranged from 0.5 to 3.0 ng/ml. At each concentration, experiments were repeated in 10−20 patients. Propofol 2 mg/kg and rocuronium 0.9 mg/kg were administrated after equilibration of plasma and effect-site target remifentanil concentration. The withdrawal movements were graded on a 4-point scale. The EC_{50} and EC_{95} of remifentanil to prevent rocuronium-induced withdrawal movements were determined by using a logistic regression model.

Results: The logistic regression model showed that the probability of preventing rocuronium-induced withdrawal movement was as follows: exp (−3.49 + 2.07 × remifentanil concentration) / (1 + exp [−3.49 + 2.07 × remifentanil concentration]). EC_{50} and EC_{95} were 1.69 ng/ml (95% confidence intervals [CIs], 1.42−1.87) and 3.11 ng/ml (95% CIs, 2.79−3.72), respectively.

Conclusions: Administration of remifentanil at an effect-site target concentration of 3.1 ng/ml could effectively prevent rocuronium-induced withdrawal movements. (Korean J Anesthesiol 2014; 66: 433-438)

Key Words: Injections, Pain, Pediatrics, Remifentanil, Rocuronium.

Introduction

Intravenous administration of rocuronium induces intense pain in most patients (60−100%) [1-3]. This pain can elicit either reflex withdrawal movements of the hand and arm where the injection site is located or generalized movements of the body in unconscious patients. During anesthesia induction, these withdrawal movements may cause dislocation of intravenous catheters, difficulties in administration of additional drugs, and subsequent risk of cardiovascular activation [4]. This is especially harmful to young children because of difficulties in rapid insertion of a catheter.

Remifentanil is a synthetic and esterase-metabolized opioid. It has a rapid onset and an ultra-short duration of action with a stable, short context-sensitive half-time [5]. Many studies have reported that remifentanil effectively reduces rocuronium-induced pain and withdrawal movements [6-9]. There have recently been studies on the EC_{50} and EC_{95} of remifentanil to prevent withdrawal movements in adults [4,10] and children [10] using the Dixon up-and-down method and by probit analysis. However, their clinical applicability may be limited because EC_{50} and EC_{95} reported in previous studies have very wide confidence intervals. This study was designed to evaluate the clinically useful EC_{50} and EC_{95} of remifentanil to prevent withdrawal movements in a large number of pediatric patients and by logistic regression analysis.

Materials and Methods

After obtaining approval from the Institutional Review Board of our hospital and written informed consent from the patients, 171 pediatric patients aged 5−12 years who were at American Society of Anesthesiology physical status I or II were enrolled. Patients with history of neurological deficits, allergies to anesthetic medications, asthma, or poor venous access, were excluded. Also, patients with severe separation anxiety who could not be delivered into the operating room without the administration of a hypnotic drug were excluded. None of the patients were premedicated with hypnotic or sedative medications before anesthesia. A 22-gauge intravenous cannula was inserted into the dorsum of the hand without subcutaneous lidocaine infiltration in the ward about 2 hours before the induction of anesthesia. Dextrose-saline solution was chosen as the intravenous fluid. On arrival at the operating room, each patient's electrocardiogram, pulse oximetric measurements, and non-invasive blood pressure were monitored, and a mask delivering 5 L/min of O_2 was loosely applied to the face. Remifentanil was administered by target-controlled infusion via a syringe pump (Pilot anesthesia 2, Fresenius vial, France) driven by STELPUMP (Ver. 1.07). The pharmacokinetics model proposed by Minto et al. [11] was

used. Effect-site target concentrations used in this experiment ranged from 0.5 to 3.0 ng/ml. Patients were divided into 10 groups according to the effect-site target remifentanil concentrations (ng/ml): the remifentanil 0.5, 1.0, 1.5, 1.8, 2.0, 2.2, 2.4, 2.6, 2.8, and 3.0 groups. At each concentration, experiments were repeated in 10−20 pediatric patients.

After equilibration of plasma and effect-site target remifentanil concentrations, propofol 2 mg/kg was administrated. During administration of remifentanil and propofol, the assistants held the patients by the arms to keep them steady if needed. Immediately after loss of consciousness and the eyelash reflex, mask ventilation was started with O_2 at 5 L/min, and 1% rocuronium was administrated at 0.9 mg/kg over 5 seconds into a port connected directly to the i.v. cannula. Withdrawal movements were observed by the same blinded investigator using a 4-point scale: 0 = no movement; 1 = movement limited to the wrist; 2 = movement limited to the arm; and 3 = generalized movement [2,6]. A grade of 2 or more was considered significant movements. The order of experiments was randomly selected, and the anesthesiologist who graded withdrawal movements was blinded to the concentrations of remifentanil used. After grading withdrawal movements, anesthesia was induced with sevoflurane 3−5 vol% and O_2 100%, and tracheal intubation was performed 90 seconds later. Anesthesia was maintained with sovoflurane 1−5 vol% and 50% nitrous oxide in oxygen. Blood pressure and heart rate were recorded upon arriving at the operation room, after reaching the effect-site target concentration of remifentanil, and immediately after intubation.

Statistical analysis

Statistical analyses were performed using SPSS 18.0 (SPSS, Chicago, IL, USA). The EC_{50} and EC_{95} of remifentanil to prevent rocuronium-induced withdrawal movements were determined by a logistic regression model. The size of the samples was 5 times as large as that of a study done by using Dixon's method [12]. In previous studies [4,10] and our preliminary study, the predicted values of EC_{20-95} ranged from 1.0 to 3.0 ng/ml. On the basis of these results, remifentanil concentration was determined as 0.5 to 3.0 ng/ml in our study.

The significance of regression coefficients was verified by the t test. The fitness for model was verified by the Pearson goodness-of-fit test. Concentration response curve was plotted using the equation obtained from the logistic regression model. Hemodynamic data were analyzed by repeated measured ANOVA, and Tukey was used for *post hoc* multiple comparisons. Values were expressed as mean ± SD, mean (95% confidence intervals [CIs]), or number of patients. A P value of < 0.05 was considered statistically significant.

Results

The demographic and hemodynamic data are shown in Table 1. There was no case of significant hypotension, bradycardia, or O_2 desaturation during remifentanil infusion. Blood pressure showed a decreasing tendency in the experiments. The remifentanil 1.5 group showed a higher mean blood pressure than the remifentanil 3.0 group (P = 0.047). Heart rate increased in all groups immediately after intubation, but there were no significant differences between the 10 groups (Fig. 1). Since the range of the hemodynamic data was very wide (Table 1), a larger number of patients is needed to evaluate the exact hemodynamic effect of various remifentanil concentrations.

To estimate the probability of preventing rocuronium-induced withdrawal movement (no response, grade of withdrawal movements 0 or 1) of various remifentanil concentrations, we fitted the experimental data to the logistic regression model. The Pearson goodness-of-fit test showed that our data fitted well to this model (P = 0.41). The logistic regression formula is as follows:

$$E(Y) = \frac{\exp(\beta_0 + \beta_1 \times X)}{[1 + \exp(\beta_0 + \beta_1 \times X)]}$$

where $\beta_0 = -3.49 \pm 0.73$;

$\beta_1 = 2.07 \pm 0.35$;

E(Y) = the probability for preventing rocuronium-induced withdrawal movement; and

X = the effect-site target concentration of remifentanil.

The regression coefficients were statistically significant (P = 0.00). EC_{50} was 1.69 (95% CIs, 1.42−1.87). EC_{95} was 3.11 (95% CIs, 2.79−3.72) (Table 2, Fig. 2).

Table 1. Demographic and Hemodynamic Data of the Patients

N	171
Gender (M/F)	105/66
Age (yr)	7.6 ± 2.1
Height (cm)	127.6 ± 15.8
Weight (kg)	29.8 ± 10.0
Before remifentanil infusion	
MAP (mmHg)	84 ± 10
HR (beats/min)	96 ± 14
At target remifentanil concentration	
MAP (mmHg)	80 ± 10
HR (beats/min)	95 ± 18
Immediately after intubation	
MAP (mmHg)	75 ± 17
HR (beats/min)	126 ± 14

Values are mean ± SD or number. MAP: mean arterial pressure, HR: heart rate.

Table 2. The Experimental and Estimated Probability of Preventing Rocuronium-induced Withdrawal Movements according to Effect-site Target Concentrations of Remifentanil

Remifentanil (ng/ml)	N of patients	N of no response	Experimental probability	Estimated probability
0.5	10	0	0.00	0.08
1.0	10	2	0.20	0.20
1.5	19	10	0.53	0.41
1.8	18	11	0.61	0.56
2.0	20	14	0.70	0.66
2.2	18	10	0.56	0.74
2.4	19	14	0.73	0.81
2.6	18	15	083	0.87
2.8	20	19	0.95	0.91
3.0	19	19	1.00	0.94

Values are number of patients or probability (0 ≤ P ≤ 1). Estimated probabilities were calculated by using the logistic regression formula.
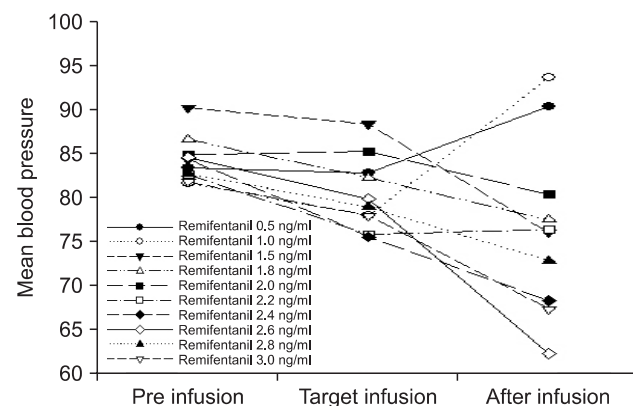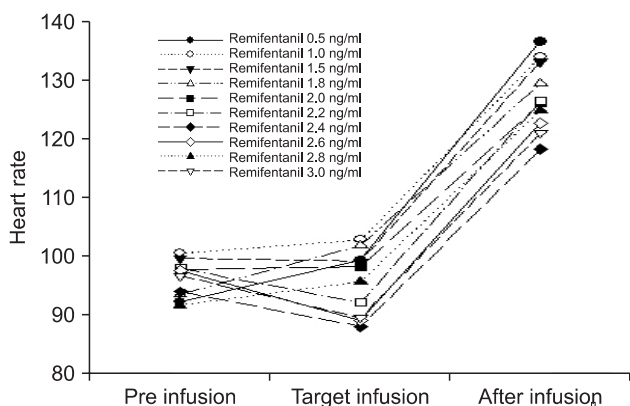

Fig. 1. Heart rate and mean arterial pressure according to remifentanil concentrations. The remifentanil 1.5 group shows a higher mean blood pressure than the remifentanil 3.0 group (P = 0.047). Heart rate increased in all groups immediately after intubation, but there were no significant differences between the 10 groups.
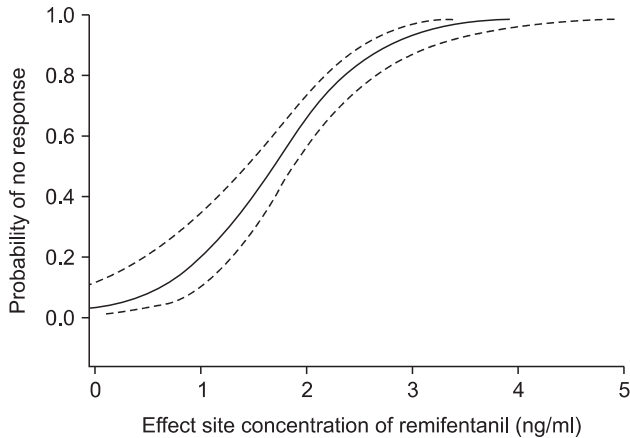
Fig. 2. Concentration-response curve and 95% confidence intervals (95% CIs) plotted from logistic regression model. EC_{50} and EC_{95} are 1.69 ng/ml (95% CIs, 1.42–1.87) and 3.11 ng/ml (95% CIs, 2.79–3.72), respectively.

Discussion

This study aimed to determine the EC_{50} and EC_{95} of remifentanil to prevent rocuronium induced withdrawal movements. Rocuronium-induced withdrawal movements are known to be associated with a severe burning pain lasting for approximately 10−20 seconds [1]. Although the pathophysiological mechanism of the pain is unclear, direct activation of the c-nociceptor by the release of local mediators has been suggested [13]. It may also be associated with the osmolality and pH of drugs [14]. However, Tuncali et al. [15] have documented that dilution of rocuronium without changes in pH or osmolality eliminates rocuronium injection pain. The algogenic effect of aminosteroidal neuromuscular blockers could be prominent because rocuronium is a less potent neuromuscular blocking drug that needs the higher dose or concentration in clinical use [13]. Rocuronium injection pain is reportedly more common in pediatric patients because small vessels require a long time to wash out [7,10].

Numerous drugs have been studied to prevent rocuronium injection pain. Lidocaine [16], bicarbonate [17], esmolol [18], ondansetron [19], epedrine [20], and opioids [6-8] are known to be effective. Kim et al. [16] have demonstrated that the lidocaine occlusion method is more effective in adults and that addition of sodium bicarbonate is more effective in children. Many studies have indicated that pretreatment with opioids could prevent rocuronium injection pain effectively [6-8]. Remifentanil seems to be suitable especially for short-duration pain control on the basis of its pharmacokinetic profile [5]. While application of a pneumatic tourniquet is useful for drugs with local anesthetic properties, including lidocaine [16] and ondansetron [19], centrally acting drugs, like opioids, require time to reach equilibrium at the effect site. Remifentanil is known to act on the central

opioid receptor rather than the peripheral opioid receptor [21]. A time interval of 90 seconds between injections of remifentanil and rocuronium is recommended for a maximal effect [21]. Remifentnil is known to have a dose-dependent effect. Kim et al. [7] reported that remifentanil 1 μg/kg was more effective in preventing rocuronium induced withdrawal movements than remifentanil 0.5 μg/kg. A few studies have reported the EC_{50} and EC_{95} of remifentanil to prevent rocuronium withdrawal movements in children [10] and adults [4,10] using the Dixon's up-and down method and by probit analysis. These studies were originally designed for Dixon's up-and down method that was suitable for calculating EC_{50}. However, the number of patients seems to be too small for probit analysis in calculating for EC_{95}. The resulting confidence interval was too wide for clinical use. The EC_{95} of remifentanil needs to be definitely established in order to be used in clinical practice. EC_{95} can be calculated with a small number of patients by using biased-coin design up-and-down method [22]. However, this method was designed to repeat experiments nearly up to target concentration. Thus, the concentration-response curve covering the wide range of concentrations may be hard to plot. By applying a logistic regression model and increasing the number of patients, we were able to reduce 95% confidence intervals to one-tenth of the value reported by a study by using Dixon's up-and-down method [4] and plot the concentration-response curve with acceptable confidence intervals. A logistic regression model is used in cases where dependent variables are discrete data. Through logistic transformation, discrete dependent variables are converted to continuous variables. As independent variables increase, the dependent variables converge to 1 [23].

The results of this study are subject to at least 2 limitations. First, this study was inadequate to evaluate the hemodynamic effect of increasing remifentanil concentration. Regardless of remifentanil concentrations (0.5−3.0 ng/ml) used in this study, heart rate increased immediately after intubation without significant differences between the individual groups with different remifentanil concentrations. The range of hemodynamic data was too wide to find any differences between the individual groups with different remifentanil concentrations. To evaluate hemodynamic response to increasing remifentanil concentrations, corresponding increases in the number of patients are required. Estimated EC_{95} for preventing rocuronium-induced withdrawal response is 3.11 ng/ml. This value is beyond the range of concentrations used by our study. Although it is uncertain whether remifentanil has a hemodynamic effect at a concentration of 3.11 ng/ ml, it is inconceivable that remifentanil led to hemodynamic disturbance. An effect-site target remifentanil concentration of 3.0 ng/ml was unable to blunt the hemodynamic response of intubation. A much higher concentration of remifentanil is needed to simultaneously prevent rocuronium-

induced withdrawal movements and hemodynamic response to intubation. Park et al. [24] reported that an effect-site target remifentanil concentration of 7.5 ng/ml improved hemodynamic stability after insertion of laryngeal mask airway [22]. Further studies are required to confirm our results. Second, Minto's pharmacokinetics model was used in this study. Minto's model was established on the basis of adult pharmacokinetic data [11]. When adult pharmacokinetics model is used in children, remifentanil blood concentration could be higher because the clearance is underpredicted [25]. Because there is a report that it is not satisfactory to use the adult pharmacokinetic model for children under 5 years [26], we limited the patient's age to be above 5 years in this study. However, Ross et al. [27] have shown that because both clearance and volume of distribution were inversely related to age, children aged >2 years have similar pharmacokinetic profiles as adults. Jeleazcov et al.[28] reported that Keo., the parameter to be vital for the prediction of effect site concentration in TCI system was similar to the values reported by Minto in children > 1 year. Although many studies of children have used Minto's pharmacokinetic model [10,24,29,30], establishment of pediatric pharmacokinetic models requires more accurate studies.

In summary, to prevent rocuronium-induced withdrawal movements in children, the EC_{50} of remifentanil was 1.69 ng/ml (95% CIs, 1.42−1.87), and EC_{95} of remifentanil was 3.11 ng/ml (95% CIs, 2.79−3.72). Administration of an effect-site target remifentanil concentration of 3.1 ng/ml could effectively prevent rocuronium-induced withdrawal movements in pediatric patients.

References

1. Borgeat A, Kwiatkowski D. Spontaneous movements associated with rocuronium: is pain on injection the cause? Br J Anaesth 1997; 79: 382-3.
2. Kim JY, Kim JY, Kim YB, Kwak HJ. Pretreatment with remifentanil to prevent withdrawal after rocuronium in children. Br J Anaesth 2007; 98: 120-3.
3. Chiarella AB, Jolly DT, Huston CM, Clanachan AS. Comparison of four strategies to reduce the pain associated with intravenous administration of rocuronium. Br J Anaesth 2003; 90: 377-9.
4. Yoon JY, Kim HK, Kwon JY, Shin SW, Kim KH, Kim WS, et al. EC(50) of remifentanil to prevent withdrawal movement associated with injection of rocuronium. J Anesth 2010; 24: 182-6.
5. Scott LJ, Perry CM. Remifentanil: a review of its use during the induction and maintenance of general anaesthesia. Drugs 2005; 65: 1793-823.
6. Oh AY, Seo KS, Goo EK, Park YO, Kim SJ, Kim JH. Prevention of withdrawal movement associated with injection of rocuronium in children: comparison of remifentanil, alfentanil and fentanyl. Acta Anaesthesiol Scand 2007; 51: 1190-3.
7. Kim JY, Kwak HJ, Kim JY, Park KS, Song JS. Prevention of rocuronium-induced withdrawal movement in children: a comparison of remifentanil with alfentanil. Paediatr Anaesth 2008; 18: 245-50.
8. Choi YJ, Park HS, Lee H, Yoon SZ. Single pretreatment of remifentanil may reduce pain after propofol and rocuronium injection in rapid sequence induction. Korean J Anesthesiol 2012; 63: 413-8.
9. Choi BI, Choi SH, Shin YS, Lee SJ, Yoon KB, Shin SK, et al. Remifentanil prevents withdrawal movements caused by intravenous injection of rocuronium. Yonsei Med J 2008; 49: 211-6.
10. Park SJ, Park HJ, Choi JY, Kang HS, Choi HS. The influence of age and gender on remifentanil EC(50) for preventing rocuronium induced withdrawal movements. Korean J Anesthesiol 2010; 58: 244-8.
11. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 1997; 86: 10-23.
12. Dixon WJ. Staircase bioassay: the up-and-down method. Nerusci Biobehav Rev 1991; 15: 47-50.
13. Blunk JA, Seifert F, Schmelz M, Reeh PW, Koppert W. Injection pain of rocuronium and vecuronium is evoked by direct activation of nociceptive nerve endings. Eur J Anaesthesiol 2003; 20: 245-53.
14. Klement W, Arndt JO. Pain on i.v. injection of some anaesthetic agents is evoked by the unphysiological osmolality or pH of their formulations. Br J Anaesth 1991; 66: 189-95.
15. Tuncali B, Karci A, Tuncali BE, Mavioglu O, Olguner CG, Ayhan S, et al. Dilution of rocuronium to 0.5 mg/mL with 0.9% NaCl eliminates the pain during intravenous injection in awake patients. Anesth Analg 2004; 99: 740-3.
16. Kim KS, Kim YS, Jeon WJ, Yeom JH. Prevention of withdrawal associated with the injection of rocuronium in adults and children. J Clin Anesth 2006; 18: 334-8.
17. Han DW, Koo BN, Choi SH, Lee JS, Shin YS, Sharma M, et al. Neutralized rocuronium (pH 7.4) before administration prevents injection pain in awake patients: a randomized prospective trial. J Clin Anesth 2007; 19: 418-23.
18. Yavascaoglu B, Kaya FN, Ozcan B. Esmolol pretreatment reduces the frequency and severity of pain on injection of rocuronium. J Clin Anesth 2007; 19: 413-7.

19. Memiş D, Turan A, Karamanlioğlu B, Süt N, Pamukçu Z. The prevention of pain from injection of rocuronium by ondansetron, lidocaine, tramadol, and fentanyl. Anesth Analg 2002; 94: 1517-20.

20. Akcaboy ZN, Akcaboy EY, Soyal OB, Turhan G, Gogus N. Can ephedrine pretreatment be effective in alleviating rocuronium injection pain? Med Princ Pract 2012; 21: 323-7.

21. Yoon JR, Jeon Y, Yoo Y, Shin HJ, Ahn JH, Lim CH. The analgesic effect of remifentanil on prevention of withdrawal response associated with the injection of rocuronium in children: no evidence for a peripheral action. J Int Med Res 2010; 38: 1795-800.

22. George RB, McKeen D, Columb MO, Habib AS. Up-down determination of the 90% effective dose of phenylephrine for the treatment of spinal anesthesia-induced hypotension in parturients undergoing cesarean delivery. Anesth Analg 2010; 110: 154-8.

23. Park SH. Regression analysis. 3rd ed. Seoul, Minyoung Publishing Co. 1998, pp 368-73.

24. Park HJ, Lee JR, Kim CS, Kim SD, Kim HS. Remifentanil halves the EC50 of propofol for successful insertion of the laryngeal mask airway and laryngeal tube in pediatric patients. Anesth Analg 2007; 105: 57-61.

25. Rigby-Jones AE, Priston MJ, Sneyd JR, McCabe AP, Davis GI, Tooley MA, et al. Remifentanil-midazolam sedation for paediatric patients receiving mechanical ventilation after cardiac surgery. Br J Anaesth 2007; 99: 252-61.

26. Anderson BJ. Pediatric models for adult target-controlled infusion pumps. Paediatr Anaesth 2010; 20: 223-32.

27. Ross AK, Davis PJ, Dear Gd GL, Ginsberg B, McGowan FX, Stiller RD, et al. Pharmacokinetics of remifentanil in anesthetized pediatric patients undergoing elective surgery or diagnostic procedures. Anesth Analg 2001; 93: 1393-401.

28. Jeleazcov C, Ihmsen H, Schmidt J, Ammon C, Schwilden H, Schüttler J, et al. Pharmacodynamic modelling of the bispectral index response to propofol-based anaesthesia during general surgery in children. Br J Anaesth 2008; 100: 509-16.

29. Kim EJ, Shin SW, Kim TK, Yoon JU, Byeon GJ, Kim HJ. The median effective effect-site concentration of remifentanil for minimizing the cardiovascular changes to endotracheal intubation during desflurane anesthesia in pediatric patients. Korean J Anesthesiol 2012; 63: 314-20.

30. Kim HS, Park HJ, Kim CS, Lee JR. Combination of propofol and remifentanil target-controlled infusion for laryngeal mask airway insertion in children. Minerva Anestesiol 2011; 77: 687-92.