Int J Clin Exp Med 2015;8(11):21235-21240
www.ijcem.com /ISSN:1940-5901/IJCEM0012437

Original Article

The optimum dose of intranasal remifentanil for laryngeal mask airway insertion during sevoflurane induction in children: a randomized controlled trial

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Received July 5, 2015; Accepted October 9, 2015; Epub November 15, 2015; Published November 30, 2015

Abstract: Objective: The purpose of this study was to determine the optimum dose of intranasal remifentanil required to produce satisfactory laryngeal mask airway (LMA) insertion conditions during inhalation induction of anesthesia using 5% sevoflurane in children. Methods: Seven-five American Society of Anesthesiologists physical status (ASA) I subjects, aged 2-5 years, scheduled for minor elective surgery were randomly allocated to receive one of five doses of intranasal remifentanil (nil, 0.25, 0.5, 0.75 and 1.0 $\mu g \cdot kg^{-1}$) during 5% sevoflurane induction. Laryngeal mask insertion was attempted 120 s after intranasal remifentanil administration and the response of subjects was classified as either 'Failure' or 'Success'. "Success" was defined as a relaxed mandible without coughing, gapping, swallowing, laryngospasm or gross purposeful movement. Secondary outcomes included the duration of apnea, hemodynamic changes and complications. Results: For each groups (nil, 0.25, 0.5, 0.75 or 1.0 $\mu g \cdot kg^{-1}$ remifentanil), the incidence of satisfactory LMA insertion conditions was 0, 33.3%, 60%, 86.7% and 100% respectively. None of subjects suffered from any serious complications such as laryngospasm,or hypotension and bradycardia. Conclusion: The ED_{50} and ED_{95} of intranasal remifentanil for successful LMA insertion in children were estimated to be 0.36 and 0.998 $\mu g \cdot kg^{-1}$ during 5% sevoflurane inhalation induction for 3 min.

Keywords: Volatile anesthetics, sevoflurane, potency, premedication, intranasal, opioid, remifentanil, laryngeal mask airway

Introduction

Inhalation induction of anesthesia with sevoflurane is an appropriate procedure for laryngeal mask airway (LMA) intubation without neuromuscular blocking drugs in children [1]. However, the excitatory phenomenon is the major disadvantages during inhalation induction technique, and high alveolar sevoflurane concentration (8%) may induce an epileptiform electroencephalogram (EEG). Thus, several experts recommend 5% sevoflurane as a safe inspired concentration for inhalation induction in children [2].

In addition, considerable evidence exist that addition of a potent and short-acting opioid (for example remifentanil) could facilitate tracheal intubation and LMA insertion [3-5]. Intranasal administration is a relatively noninvasive and easy route, which can be particularly advantageous when an anesthesiologist prefers to LMA intubation before establishing IV access to administrate adjuvant drugs.

To date, the optimal dose of intranasal remifentanil during inhalation induction with sevoflurane in pediatric anesthesia has not been established. Thus, we performed this study to determine the 50% effective dose (ED_{50}) and 95% effective dose (ED_{95}) of intranasal remifentanilto provide ideal LMA insertion conditions in children during 5% sevoflurane induction.

Methods

After obtaining ethical approval from Fujian Provincial Hospital (Reference K2013-05-003), this prospective randomized, double-blind trial was conducted at Fujian Provincial Hospital fr-

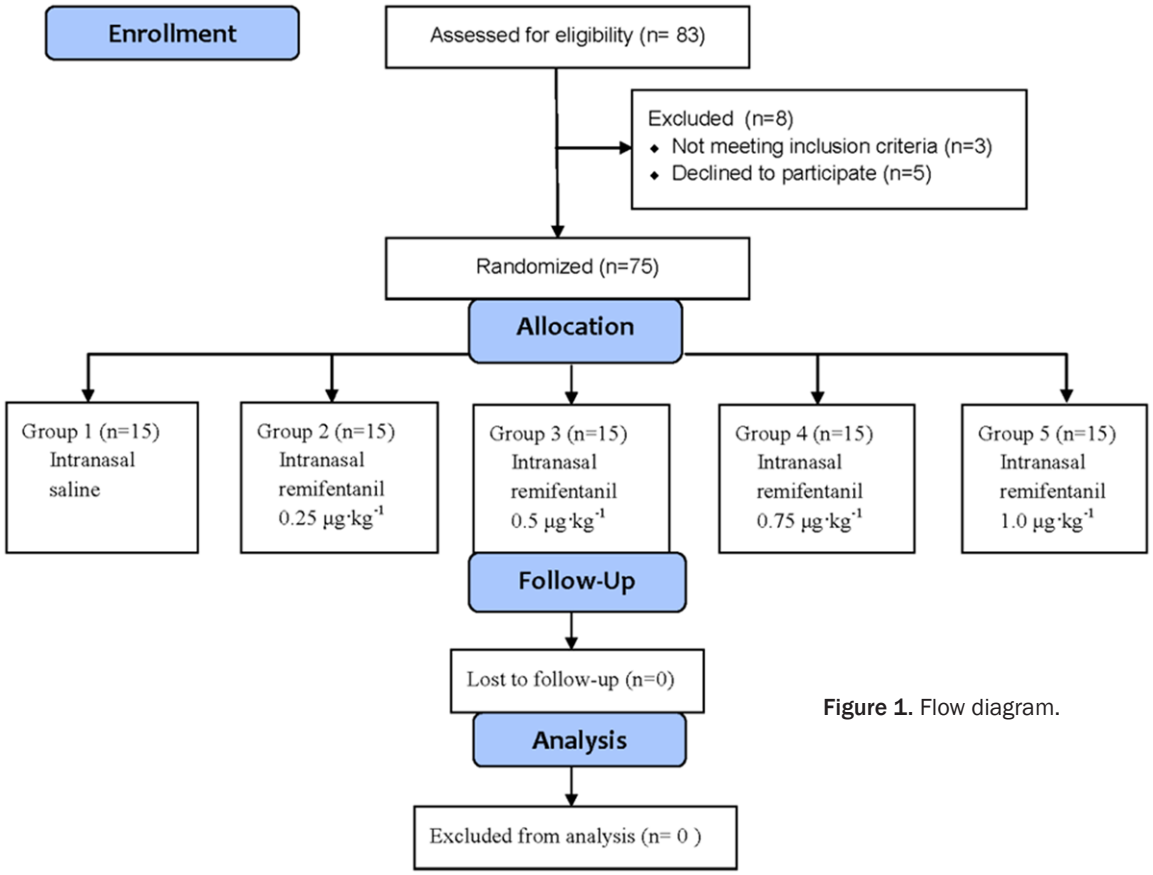

Figure 1. Flow diagram.

Table 1. Demographic and clinical characteristics

	Remifentanil dose (μg·kg^{-1})				
	Nil	0.25	0.5	0.75	1.0
Gender; (M/F)	10:5	10:5	9:6	11:4	10:5
Age (years)	3.3 (1.2)	3.2 (1.4)	3.4 (1.0)	3.3 (1.3)	3.2 (1.2)
Weight (kg)	16.5 (5.2)	17.3 (4.6)	17.9 (4.3)	16.9 (4.8)	17.6 (4.5)
Height (cm)	97.2 (4.3)	97.9 (5.7)	96.4 (4.6)	95.4 (5.4)	96.7 (4.1)

Values are mean (SD) or numbers.

om June 2013 to December 2013. Our study protocol was in line with the principles of the Declaration of Helsinki. Seventy-five subjects aged 2 to 5 with American Society of Anesthesiologists physical status (ASA) I, who underwent elective mirror surgery were recruited in our study. The exclusion criteria included potentially difficult airway, acute upper respiratory tract infection, asthma and gastroesophageal reflux. Written informed consent was obtained from the parent or legal guardian before randomization. Subjects were randomly and equally assigned to five groups by a table of computer-generated random numbers. Group assignments were sealed in sequentially numbered opaque envelopes.

All subjects were starved at least 6 h but not premedicated. Upon arrival in the operating room, electrocardiogram, pulse oximetry (SpO_2), gas analyzer and noninvasive arterial blood pressure (NIBP) were monitored in all subjects. The inspired and end-tidal concentrations of sevoflurane, carbon dioxide, and oxygen were continually measured and recorded by the side stream-type infrared multi-analyzer, which was calibrated before each use and the accuracy of which is ±0.1%. General anesthesia was induced using a face mask via asemi closed anesthetic circuit primed with 5% sevoflurane in 100% oxygen. The fresh gas flow was set at a flow rate of 6 L/min. After sevoflurane was inhaled for 1 minutes and the eyelash reflex disappeared, one of five doses of intranasal remifentanil (nil, 0.25, 0.5, 0.75 and 1.0 μg·kg^{-1}) was administered via intranasal mucosal atomization device (LMA MAD Nasal™, Wolfe Tory Medical INC, USA). Intranasal medication was prepared in a 1-mL syringeby a research nurse who was not involved inobservation of the patient's

Table 2. Patients'induction profiles

	Remifentanil dose (μg·kg^{-1})					*P* value
	Nil	0.25	0.5	0.75	1.0	
Swallowing; n	5	3	1	0*	0*	0.018
Gapping and coughing; n	4	2	1	0	0	0.085
Movement; n	6	5	4	2	0*,#	0.049
Apnea time; second	58 (11)	82 (15)	125 (21)	163 (26)*,#	204 (31)*,#	0.032
Upper airway trauma; n	5	3	1	2	0*	0.11

Values are numbers or mean (SD), *P<0.05 versus Group nil, #P<0.05 versus Group 0.25.

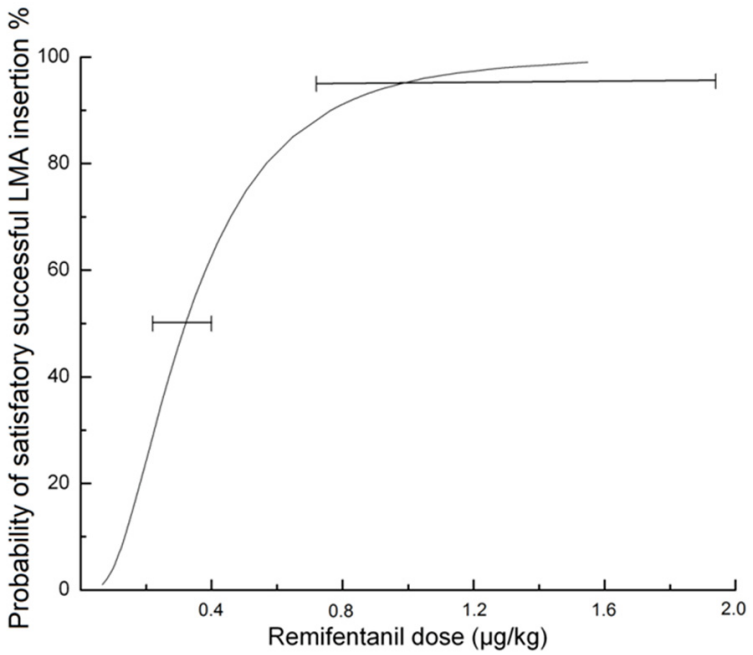

Figure 2. Dose-response curve from the probit analyses ofindividual remifentanil dose and the reaction to LMA insertion in the patients. The dose of remifentanil at which therewas a 50% and 95% probability of satisfactory LMA insertion was 0.36 and 0.998 μg·kg^{-1}, respectively.

responses. Anesthesia induction continued with 5% sevoflurane and ventilation was assisted manually to maintain the end-tidal carbon dioxide partial pressure at 35-40 mmHg. Three minutes after 5% sevoflurane induction, a classic LMA (Unique™, The Laryngeal Mask Company Limited, Singapore) was inserted by a single anesthesiologist who was unaware of the dose assignment using the technique recommended by Brain et al. [6]. LMA insertion was classified as "Failure" and "Success". "Success" was defined as a relaxed mandible without coughing, gapping, swallowing, laryngospasm or gross purposeful movement. If the LMA insertion was "Failure", lung ventilation was performed via the face mask with 5% sevoflurane and IV access was established at the same time, then propofol 2 mg·kg^{-1} was administered to facilitate another LMA intubation.

The primary outcome was the response to LMA insertion, which included development of gross purposeful movement, coughing, gagging, inadequate jaw relaxation (clenching), and upper airway obstruction such as laryngospasm. The response of the subject was observed until 1 min after LMA insertion and evaluated as failure or success.

Failure was defined as any of the above mentioned responses. Secondary outcomes included the duration of apnea and hemodymic changes. Duration of apnea was evaluated by endtidal capnography from LMA insertion to restoration of spontaneous respiration. The subjects' MAP and HR were recorded before induction, one minute before and after LMA insertion.

Our sample size calculation for the two-tailed testing was based on the satisfaction of LMA insertion by the statistical software package NQUERY ADVISOR (version 4.0,Janet D Elashoff, USA). A type I error estimate of 5% (α = 0.05) and a power (1-β) of 80% indicated that a sample of 13 subjects pergroup would be required. Allowing for an approximately 15% incomplete followup or dropout, a total of 75 subjects were enrolled in this study. Statistical analysis was performed by SPSS version 19.0 (SPSS Inc., Chicago, USA). The normality of distribution was assessed by the Kolmogorov-Smirnov test.

Table 3. Hemodynamicresponse to LMA insertion

	Remifentanil dose (μg·kg^{-1})				
	Nil	0.25	0.5	0.75	1.0
Mean arterial pressure; mmHg					
Before induction	80 (9)	83 (8)	81 (9)	82 (7)	80 (8)
Before LMA insertion	79 (11)	78 (9)	76 (8)	74 (10)	75 (9)
1 min after LMA insertion	90 (9)*	84 (8)	85 (9)	81 (11)	70 (8)#
Heart rate; beats·min^{-1}					
Before induction	96 (11)	95 (12)	94 (13)	97 (14)	96 (13)
Before LMA insertion	101 (9)	99 (13)	92 (10)	89 (12)	91 (11)
1 min after LMA insertion	127 (14)*	116 (12)*	111 (12)*	92 (10)#	89 (10)#

Values are mean (SD), *P<0.05 versus before induction, #P<0.05 versus Group nil.

Parametric data were analyzed with the independent t-test and were reported as mean (standard deviation [SD]). Nonparametricdata were reported as median (interquartilerange [IQR]) and analyzed using the Mann-Whitney U-test. The goodness-of-fit was performed by the probit analysis (linear regression plot of log dose vs. percentage response). A P value of less than 0.05 was considered to be statistically significant.

Results

We initially assessed 83 subjects for eligibility to participate in thisstudy (**Figure 1**). Of these, 3 subjects did not meet the inclusion criteria, 5 declined to participate, and the remaining 75 subject senrolled to the study. As showed in **Table 1**, subjects' demographic and clinical characteristics were comparable with respect to age, weight, gender and height.

The subjects' responses to LMA insertion were shown in **Table 2**. For each groups (nil, 0.25, 0.5, 0.75 or 1.0 μg·kg^{-1} remifentanil), the incidence of satisfactory LMA insertion conditions was 0, 33.3%, 60%, 86.7% and 100% respectively. A dose-response relation of remifentanil for LMA insertion is illustrated by the curve constructed from the probit test data (**Figure 2**), the median effective dose (ED_{50}) of intranasal remifentanil during 5% sevoflurane induction for satisfactory LMA insertion was 0.36 μg·kg^{-1} (95% confidence intervals, 0.241-0.456 μg·kg^{-1}), and the 95% effective dose (ED_{95}) of intranasal remifentanil was 0.998 μg·kg^{-1} (95% confidence intervals, 0.726-1.955 μg·kg^{-1}).

Hemodynamic responses to LMA insertion were shown in **Table 3**. Baseline MAP and HR were similar with no statistical significance among five groups. None of the subjects required atropine as a rescue therapy for bradycardia (HR<60 bpm). None of the subjects suffered oxygen desaturation (SpO_2<90%) during the study.

Discussion

The main finding of our study is that intranasal remifentanil can improve the insertion of LMA after the induction under inhalational anesthesia with sevoflurane in pediatric subjects. From probit analysis, the dose of intranasal remifentanil in 50% and 95% of children under 5% sevoflurane induction were 0.36 μg·kg^{-1} (95% confidence intervals, 0.241-0.456 μg·kg^{-1}) and 0.998 μg·kg^{-1} (95% confidence intervals, 0.726-1.955 μg·kg^{-1}), respectively. During the study period, none of subjects suffered from any serious complications such as laryngospasm, or hypotension and bradycardia.

A vital capacity inhalation induction technique with high-concentration sevoflurane has been used for the rapid and smooth insertion of LMA [7, 8]. When used alone in unpremeditated pediatric, the EC_{50} and EC_{95} of sevoflurane were 1.57% and 2.22% for LMA insertion [9]. However, inherent vices such as delayed jaw relaxation and a relatively longer time for LMA insertion limit its application. In this study, LMA intubation was attempted 3 min following the start of induction with a mean end-tidal sevoflurane concentration of 3.2%. One reason for the discrepancy between the values reported in the literature and the findings of the present study might be the different study designs.

Our results are broadly consistent with previous work. The addition of remifentanil during sevoflurane inhalational induction has been reported to allow rapid tracheal intubation without the use of neuromuscular blocking agents in adult and pediatric [10, 11]. Our data further confirmed that the improvement of condition for LMA intubation when intranasal remifentanil was added to sevoflurane induction. This effect of opioids may be due to the blockade of afferent nerve impulses resulting from stimulation of the pharynx and the larynx [12] and improve the jaw relaxation [13]. In our study, we

chose intranasal remifentanil as adjuncts for anesthesia induction, as the intranasal approach is fast, effective and easy to facilitate. Intranasal absorption is very rapid as aresult of the large surface area and vascularity of the nasalmucosa. The absolute bioavailability of intranasal remifentanil has been estimated at 50% in pediatric subjects [14]. With intranasal remifentanil and inhalational sevoflurane, anesthesiologists may be liberated from difficult venous establishment for pediatric subjects.

Because the depth of anesthesia at the time of LMA intubation can influence conditions for LMA intubation, we standardized the induction technique in the present study. As the peak effect of remifentanil is achieved approximately 90 s after IV administration [10], we arbitrary adopted 120 s after intranasal administration as the time for inserting LMA. Though remifentanil may cause adverse cardiovascular effects, such as bradycardia and hypotension [15], no bradycardia or hypotension were observed in our study. Moreover, none of the subjects experienced muscle rigidity or hypoxemia during induction and all subjects' lungs were easily ventilated manually in this study. Which may be due to the dose we given was relatively small and our subjects were all in ASA I, additionally, the intrinsic muscle relaxing properties of sevoflurane may obtund the adverse effects of remifentanil.

The median effective dose (ED_{50}) is the most widely used measure of potency for drugs. Although ED_{50} corresponds to the inflection point where the slope is steepest and provides a sensitive measure of effect, the ED_{95} would often be more clinically relevant. In previous studies, the up-and-down method was used which only allows ED_{50} to be measured, however, the precision of the estimation may be changed according to the sample size [16]. Thus, we chose the bliss method to estimate the ED_{50} and ED_{95} of intranasal remifentanil in our study, which is more rigorous and reliable. We predicted ED_{95} by simple extrapolation of the probit regressioncurve, which resulted in larger confidence intervals.

There are some limitations in this study. Firstly, the time for 5% sevoflurane induction is only 3 min in our study. The LMA insertion was performed without maintenance enough time (at least 10 min) of the end-tidal concentration of sevoflurane to allow for equilibrium of alveolar and brain sevoflurane partial pressure [9, 17]. However, the more rapid increasing speed of alveolar concentration in children and the low blood-gas coefficients of sevoflurane may accelerate the equilibration for LMA insertion [18]. In busy clinical settings, the rapid induction technique has practical advantages. Secondly, the estimated ED_{50} and ED_{95} of remifentanil are limited to thespecific concentration of sevoflurane (5% sevoflurane induction for 3 min). The mean end-tidal sevoflurane concentration was 3.2%, at which the LMA insertion was attempted. Therefore, the value of sevoflurane in the currentstudy seems to be an adequate dose for induction in pediatric subjects. Thirdly, we didn't measure the actual serum concentrations of remifentanil in this study. Finally, these results should not be extrapolated to older children or adults.

In conclusion, our study have demonstrated that intranasal remifentanil to provide ideal LMA insertion conditions under the anesthetic induction with 5% sevoflurane in children, and 1 $\mu g \cdot kg^{-1}$ intranasal remifentanil appears to represent the optimum clinical dose for successful LMA insertion.

Acknowledgements

This study was supported in part by Natural Science Foundation of Fujian Province (2015-J01373). We would like to thank Professor Hong Qiu (Department of Pediatric Surgery, Fujian Provincial Hospital, Fuzhou, China) and Xiaolan Zhang (Department of Surgical Nursing, Fujian Provincial Hospital, Fuzhou, China), for their assistance.

Disclosure of conflict of interest

None.

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