J Anesth (2011) 25:195–199
DOI 10.1007/s00540-011-1092-9

ORIGINAL ARTICLE

The effect of ketamine on tracheal intubating conditions without neuromuscular blockade during sevoflurane induction in children

Kyong Sik Kim · Hyun Jeong Kwak · Sang Kee Min · Sook Young Lee · Kyung Mi Kim · Jong Yeop Kim

Received: 4 February 2010 / Accepted: 4 January 2011 / Published online: 15 February 2011

Abstract
Purpose The purpose of this study was to investigate the effect of ketamine on intubating conditions for tracheal intubation during anesthesia induction with sevoflurane and alfentanil in pediatric patients.
Methods After obtaining parental consents, 50 children, aged 3–10 years, were randomly allocated into two groups to receive either i.v. ketamine 0.5 mg/kg (ketamine group, $n = 25$) or i.v. saline 5 ml (control saline group, $n = 25$). One minute after injection of the study drug (ketamine or saline), anesthesia was induced with 5% sevoflurane, followed by injection of alfentanil 10 μg/kg 1 min later. The trachea was intubated 4 min after inhalational induction of anesthesia. Acceptable intubation was defined as excellent or good intubating conditions. Mean arterial pressure (MAP) and heart rate (HR) were recorded during the induction period.
Results The percentage of patients with acceptable intubating conditions was higher in the ketamine group (87%) than in the control group (52%) ($P = 0.0129$). MAP before intubation was significantly lower in the control group than in the ketamine group ($P = 0.001$).
Conclusion This study demonstrated that administration of ketamine 0.5 mg/kg could improve intubating conditions for tracheal intubation without neuromuscular blockade and preserve hemodynamic stability during sevoflurane inhalation induction with alfentanil in children.

Keywords Inhaled anesthetics · Ketamine · Tracheal intubating conditions

K. S. Kim
Department of Anesthesiology and Pain Medicine, Himchan Hospital, Incheon, Korea

H. J. Kwak
Department of Anesthesiology and Pain Medicine, Gachon University of Medicine and Science, Gil Medical Center, Incheon, Korea

S. K. Min · S. Y. Lee · K. M. Kim · J. Y. Kim (✉)
Department of Anesthesiology and Pain Medicine, Ajou University School of Medicine, San 5, Wonchon-dong, Yeongtong-gu, Suwon 443-721, Korea
e-mail: kjyeop@ajou.ac.kr

Introduction

Sevoflurane is frequently used for inhalation induction of anesthesia and tracheal intubation in children without use of neuromuscular blocking drugs [1]. Addition of an opioid during sevoflurane inhalation induction has been shown to provide good to excellent intubating conditions and allow rapid tracheal intubation without neuromuscular blockade [2, 3]. In addition, opioids decrease the target cerebral concentration of sevoflurane needed to perform tracheal intubation in children [4]. In a recent previous study, the effective bolus dose of alfentanil for successful tracheal intubation was 11.5 μg/kg in 50% of children during inhalation induction using sevoflurane 5% and oxygen 100% without a neuromuscular blocking agent [5]. Although the higher dose of alfentanil could improve conditions for tracheal intubation, it could cause a greater decrease in mean arterial pressure, particularly before tracheal intubation. Therefore, co-administration of different sedatives might be clinically beneficial.

Ketamine has demonstrated synergy with volatile anesthetics at the minimum alveolar concentration (MAC) in animal studies [6, 7]. In addition, Topcuoglu et al. [8] demonstrated that co-administration of ketamine was shown to improve intubating conditions during propofol–

rocuronium induction. They suggested that ketamine could provide deep anesthesia and obtund airway reflexes favoring intubating conditions. This property suggested to us the hypothesis that the addition of ketamine to sevoflurane inhalation induction would improve intubating conditions while reducing hemodynamic compromise during sevoflurane induction. To date, there have been no reports of the effect of ketamine on intubating conditions for tracheal intubation during sevoflurane induction. Therefore, the purpose of this study was to investigate the effect of ketamine on intubating conditions and hemodynamics for tracheal intubation without neuromuscular blockade during anesthesia induction with sevoflurane and alfentanil in pediatric patients.

Table 1 Assessment of intubation conditions

Variables	Intubating conditions		
	Acceptable		Unacceptable
	Excellent	Good	Poor
Ease of laryngoscopy (jaw relaxation)	Easy	Fair	Difficult
Vocal cord position	Adducted	Intermediate	Closed
Vocal cord movement	None	Moving	Closing
Airway reaction (coughing)	None	Diaphragm	Sustained
Movement of the limbs	None	Slight	Vigorous

Excellent, all criteria are excellent; good, all criteria are either excellent or good; poor, presence of a single criterion listed under 'Poor'

Materials and methods

This study was approved by the institutional review board, and written informed consent for the study was obtained from the parents of all children enrolled in the study. Fifty-five children, American Society of Anesthesiologists physical status I or II, aged 3–10 years, who were undergoing general anesthesia for short elective surgery were enrolled in this study. Children with a history of airway disease, sleep apnea, developmental delay, psychological disorders, or those who were crying on arrival in the operating room were excluded. Three children were excluded because of crying and two because of upper respiratory tract infection. Using computer-generated random numbers, a total of 50 patients were randomly allocated into two groups to receive either i.v. normal saline (control group, $n = 25$) or i.v. ketamine 0.5 mg/kg (ketamine group, $n = 25$). Patients, anesthesia providers, and investigators who assessed the intubation conditions were blinded to the treatment group, and an independent researcher prepared the study solution consisting of a 5-ml mixture of ketamine 0.5 mg/kg and normal saline in the ketamine group and 5 ml normal saline in the control group.

Before patients arrived in the operating room, a 24-gauge cannula was inserted in the dorsum of the hand, and a dextrose/saline solution was infused. Once in the operating room, all patients were monitored with electrocardiogram, pulse oximeter, and a noninvasive blood pressure device. End-tidal concentration of CO_2 and sevoflurane were measured continuously at the elbow of the breathing circuit using a precalibrated gas monitor (at a sampling flow rate of 250 ml/min). Glycopyrrolate 0.004 mg/kg was administered before induction of anesthesia. One minute after injection of the study drug (ketamine or saline), anesthesia was induced via a face mask with a semiclosed anesthetic circuit primed with 5% sevoflurane in 100% oxygen for 2 min. The fresh gas flow was set to 5 l/min. Initially, patients breathed spontaneously, and ventilation was manually assisted to maintain an end-tidal CO_2 of 32–36 mmHg. One minute after induction of anesthesia, alfentanil 10 μg/kg was injected over 15 s. Four minutes after inhalational induction of anesthesia, the trachea was intubated with a cuffed tracheal tube. Intubation conditions were evaluated according to a scoring system described by Viby-Mogensen et al. [9] (Table 1). Acceptable intubation was defined as excellent or good intubating conditions. Any evidence of chest wall rigidity, such as difficulty in ventilation, wheezing, change in compliance, or any change in the slope of the end-tidal CO_2 waveform was noted. Arterial desaturation was defined as peripheral oxygen saturation (SpO_2) less than 90%. The clinically significant hypotension and bradycardia were defined as more than 30% decrease in the mean arterial pressure (MAP) and heart rate (HR) compared to baseline value at anesthetic induction, respectively. Rocuronium 0.3 mg/kg was administered before the second attempt in case of unacceptable intubating condition caused by the patients' strong movement, inadequate jaw relaxation, closed vocal cords, or sustained coughing. Laryngospasm was treated with propofol 0.5 mg/kg. Arterial desaturated patients were ventilated with 100% oxygen. Clinically significant hypotension and bradycardia were treated with atropine or ephedrine where appropriate. Mean arterial pressure and heart rate were recorded on arrival in the operating room (baseline, T0), after injection of the study drug (T1) and alfentanil (T2), before intubation (T3), and 1 and 3 min after intubation (T4 and T5).

Based on a previous study [5], we expected that the success rate of tracheal intubation in the control group would be 50% and that improvement in incidence would be 90% with a bolus dose of ketamine. This study was powered to detect such a reduction with type I error of 0.05 (two-tailed) and desired power of 0.9. Based on these

Table 2 Patient characteristics

	Control ($n = 25$)	Ketamine ($n = 23$)
Age (years)	7.3 ± 1.9	6.6 ± 2.3
Weight (kg)	26 ± 9	29 ± 10
Sex (M/F)	13/12	12/11
Induction profile		
Intubation time (s)	26 ± 3	25 ± 4
LOC time (s)	54 ± 11	39 ± 8*
Etsevo (vol%)	3.9 ± 0.1	4.0 ± 0.2
Induction episodes		
Cough	2	1
Chest wall rigidity	1	0
Excitatory movement	10	1*

Values are expressed as mean ± SD or number of patients

LOC, loss of consciousness; Etsevo, end-tidal sevoflurane concentration before intubation

* $P < 0.05$, versus control group

Table 3 Intubation conditions

	Control ($n = 25$)	Ketamine ($n = 23$)
Acceptable		
Total	13	20*
Excellent	6	9
Good	7	11
Unacceptable		
Total	12	3
Succeeded	4	3
Failed	8	0
Cause of failure		
Difficult laryngoscopy	4	0
Closed vocal cord	4	0
Airway reaction	4	3

Values are expressed as number of patients

* $P < 0.05$, versus control group

assumptions, 21 patients per group were required. We assumed a dropout rate of 20% and increased the sample size to 25 patients per group.

Values were expressed as mean ± SD or as number of patients (%). Statistical analyses were performed using the statistical package (SPSS 13.0 for Windows; SPSS, Chicago, IL, USA). Distribution of data was determined using Kolmogorov–Smirnov analysis. Differences between the groups were evaluated using independent sample *t* test and chi-square test where appropriate. Hemodynamic variables were analyzed using repeated-measures analysis of variance (ANOVA) and then the Bonferroni correction. A P value <0.05 was considered significant.

Results

A total of 48 patients were included in this study; 2 were excluded from analysis because of i.v. occlusion and unexpectedly difficult intubation resulting from subglottic stenosis. There were no significant differences in patient characteristics between the two groups. Mean end-tidal sevoflurane concentration was similar at intubation between the two groups. Excitatory movement during induction was more frequent in the control group than in the ketamine group ($P = 0.0049$) (Table 2).

The overall intubating condition was regarded as clinically acceptable in 13 of 25 (52%) children in the control group and in 20 of 23 (87%) in the ketamine group, and there was a significant difference between the two groups in regard to acceptable intubating conditions ($P = 0.0129$) (Table 3). Excellent overall intubating conditions were present in 6 of 25 (24%) children in the control group and in 9 of 23 (39%) children in the ketamine group. Although there were no failed intubations in the ketamine group, tracheal intubation failed in 8 children in the control group. Tracheal intubation failed in 4 of 8 children because of difficult laryngoscopy and in 4 of 8 children as a result of closed vocal cords.

MAP and HR during anesthesia induction are shown in Table 4. At T2 and T3, MAP was significantly lower in the control group than in the ketamine group ($P = 0.001$). Compared with baseline values (T0), MAP decreased significantly at T2 and T3 in the control group. HR was not significantly different at all time points between the two groups. Compared with baseline values, HR increased after tracheal intubation (T4 and T5) in both groups, although only the ketamine group showed statistical significance. There were no episodes of bradycardia or hypotension requiring treatment during the study. No patents suffered from desaturation, truncal rigidity, or laryngospasm throughout the study. One patient in the control group had vomiting and one patient in the ketamine group had nausea in the postanesthetic care unit. There was no difference in the incidence of side effects between the groups.

Discussion

This study demonstrated that administration of ketamine 0.5 mg/kg could increase the percentage of overall acceptable conditions for tracheal intubation without neuromuscular blockade during sevoflurane inhalation induction in children.

Tracheal intubation without neuromuscular blocking drugs may be used in cases where tracheal intubation is necessary but prolonged muscle relaxation is not, such as in

Table 4 Mean arterial pressure (MAP) and heart rate (HR) during anesthesia induction

	T0	T1	T2	T3	T4	T5
MAP						
Control	83.7 ± 10.9	79.6 ± 8.5	66.7 ± 7.9†	59.7 ± 5.6†	79.5 ± 12.0	75.5 ± 7.9
Ketamine	81.8 ± 11.4	87.6 ± 9.9	76.2 ± 8.3*	69.6 ± 10.3*	76.4 ± 14.3	76.6 ± 10.6
HR						
Control	101.5 ± 14.5	98.8 ± 17.3	102.2 ± 21.0	101.2 ± 19.6	121.8 ± 23.8	120.2 ± 23.1
Ketamine	98.3 ± 17.9	103.0 ± 19.6	102.8 ± 17.3	104.2 ± 19.7	116.3 ± 18.6†	116.3 ± 18.5†

Values are expressed as mean ± SD

T0, baseline (before induction); T1, after test drug (ketamine or saline) injection; T2, after alfentanil injection; T3, before intubation; T4, 1 min after intubation; T5, 3 min after intubation

* $P < 0.05$, versus control group

† $P < 0.05$, versus baseline values (T0) within the group

short surgical procedures. We enrolled patients undergoing frenotomy, adenoidectomy, and tonsillectomy, in which total anesthetic time was less than 60 min. One advantage of the sevoflurane and alfentanil induction technique is that spontaneous ventilation is maintained until alfentanil is administrated. When difficult intubation is anticipated or airway obstruction occurs, this technique is favored over intravenous induction.

Several studies have reported on tracheal intubation conditions during induction of sevoflurane inhalation with variable opioid agents without neuromuscular blockade in children [2, 4]. Min et al. [2] reported that the bolus dose of remifentanil required for successful tracheal intubation was 0.56 ± 0.15 μg/kg in 50% of children during inhalation induction using 5% sevoflurane in the absence of neuromuscular blocking drugs. In addition, the effective dose of sufentanil required for excellent intubation conditions was 0.11 ± 0.07 μg/kg at end-tidal sevoflurane of 3.5% for 50% of children [4]. Considering the equipotent dose of each opioid agent, their results were consistent with the results of this study. In this study, incidence of acceptable intubating conditions was 52% after 5% sevoflurane inhalation induction with alfentanil 10 μg/kg in children without neuromuscular blockade.

Ketamine has direct relaxant effects on airway smooth muscle [10]. It has been reported that intubation was successful in 65.5% of injured patients in the field following ketamine 2 mg/kg [11]. Therefore, we speculated that addition of ketamine would improve intubation conditions during sevoflurane and alfentanil induction. In this study, ketamine significantly increased the percentage of acceptable intubating conditions from 52% to 87%. In contrast with the results of this study, Begec et al. [12] demonstrated that ketamine 0.5 mg/kg slightly increased the percentage of acceptable intubating conditions without statistical significance. This result may be associated with anesthetic interactions with ketamine. Ketamine clearly demonstrated synergy with volatile anesthetics on minimum alveolar concentration in animal studies [6, 7]. On the other hand, propofol and ketamine reportedly interact additively to produce hypnosis and immobility in humans [13].

Ketamine has the effect of sympathetic stimulation leading to increases in myocardial contractility and vascular resistance, which in turn lead to increased arterial pressure and heart rate [14, 15]. Park et al. [16] suggested that coadministration of ketamine and glycopyrrolate might have influenced the relative lack of significant hypotension and bradycardia during sevoflurane inhalation induction with remifentanil in children. Therefore, we assumed that administration of ketamine before induction with sevoflurane and alfentanil would provide greater hemodynamic stability during anesthesia induction. This study demonstrated that MAP was significantly higher in the ketamine group than in the control group at T2 and T3 and that a low dose of ketamine could preserve hemodynamic stability before tracheal intubation. In addition, in this study, there was no severe bradycardia or hypotension during induction, even in the control group. This result may be associated with premedication with glycopyrrolate for all children.

Primary concerns regarding addition of ketamine included an increase in secretions and emergence reactions. In our study, these complications were not observed in children who received a subhypnotic dose of ketamine. Another concern limiting the use of ketamine is the possibility of increasing intracranial pressure (ICP); however, the clinical use of ketamine under controlled ventilation has gradually gained acceptance in anesthetized or brain-injured patients. Recent studies show no adverse effects of ketamine on ICP, cerebral blood flow velocity [17, 18].

One of the limitations in this study is the low acceptable intubation condition rate of the control group. Although the higher dose of alfentanil could improve the intubation conditions of the control group in children, we have been concerned about hemodynamic instability and chest wall

rigidity before tracheal intubation during sevoflurane induction with higher doses. In a previous study, the higher dose of alfentanil (15 μg/kg) was reported to cause significant decrease in MAP and HR before intubation during propofol induction in children [19]. Further studies exploring the effect of ketamine in improving intubation conditions and hemodynamic instability during sevoflurane induction with the higher doses of opioids without muscle relaxant are justified.

In conclusion, addition of ketamine could improve intubating conditions for tracheal intubation without a neuromuscular blocking agent and preserve hemodynamic stability during sevoflurane inhalation induction with alfentanil in children.

References

1. Simon L, Boucebci KJ, Orliaguet G, Aubineau JV, Devys JM, Dubousset AM. A survey of practice of tracheal intubation without muscle relaxant in paediatric patients. Paediatr Anaesth. 2002;12:36–42.
2. Min SK, Kwak YL, Park SY, Kim JS, Kim JY. The optimal dose of remifentanil for intubation during sevoflurane induction without neuromuscular blockade in children. Anaesthesia. 2007;62:446–50.
3. Verghese ST, Hannallah RS, Brennan M, Yarvitz JL, Hummer KA, Patel KM, He J, McCarter R. The effect of intranasal administration of remifentanil on intubating conditions and airway response after sevoflurane induction of anesthesia in children. Anesth Analg. 2008;107:1176–81.
4. Soulard A, Babre F, Bordes M, Meymat Y, Sztark F, Cros AM. Optimal dose of sufentanil in children for intubation after sevoflurane induction without neuromuscular block. Br J Anaesth. 2009;102:680–5.
5. Kwak HJ, Kim JY, Min SK, Kim JS, Kim JY. Optimal bolus dose of alfentanil for successful tracheal intubation during sevoflurane induction with and without nitrous oxide in children. Br J Anaesth. 2010;104:628–32.
6. Solano AM, Pypendop BH, Boscan PL, Ilkiw JE. Effect of intravenous administration of ketamine on the minimum alveolar concentration of isoflurane in anesthetized dogs. Am J Vet Res. 2006;67:21–5.
7. Hendrickx JF, Eger EI II, Sonner JM, Shafer SL. Is synergy the rule? A review of anesthetic interactions producing hypnosis and immobility. Anesth Analg. 2008;107:494–506.
8. Topcuoglu PT, Uzun S, Canbay O, Pamuk G, Ozgen S. Ketamine, but not priming, improves intubating conditions during a propofol–rocuronium induction. Can J Anaesth. 2010;57:113–9.
9. Viby-Mogensen J, Engbaek J, Eriksson LI, Gramstad L, Jensen E, Jensen FS, Koscielniak-Nielsen Z, Skovgaard LT, Ostergaard D. Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. Acta Anaesthesiol Scand. 1996;40:59–74.
10. Cheng EY, Mazzeo AJ, Bosnjak ZJ, Coon RL, Kampine JP. Direct relaxant effects of intravenous anesthetics on airway smooth muscle. Anesth Analg. 1996;83:162–8.
11. Gofrit ON, Leibovici D, Shemer J, Henig A, Shapira SC. Ketamine in the field: the use of ketamine for induction of anaesthesia before intubation in injured patients in the field. Injury. 1997;28:41–3.
12. Begec Z, Demirbilek S, Ozturk E, Erdil F, Ersoy MO. Remifentanil and propofol for tracheal intubation without muscle relaxant in children: the effects of ketamine. Eur J Anaesthesiol. 2009;26:213–7.
13. Hui TW, Short TG, Hong W, Suen T, Gin T, Plummer J. Additive interactions between propofol and ketamine when used for anesthesia induction in female patients. Anesthesiology. 1995;82:641–8.
14. White PF. Comparative evaluation of intravenous agents for rapid sequence induction-thiopental, ketamine, and midazolam. Anesthesiology. 1982;57:279–84.
15. Guit JB, Koning HM, Coster ML, Niemeijer RP, Mackie DP. Ketamine as analgesic for total intravenous anaesthesia with propofol. Anaesthesia. 1991;46:24–7.
16. Park KS, Park SY, Kim JY, Kim JS, Chae YJ. Effect of remifentanil on tracheal intubation conditions and haemodynamics in children anaesthetised with sevoflurane and nitrous oxide. Anaesth Intensive Care. 2009;37:577–83.
17. Bourgoin A, Albanèse J, Wereszczynski N, Charbit M, Vialet R, Martin C. Safety of sedation with ketamine in severe head injury patients: comparison with sufentanil. Crit Care Med. 2003;31:711–7.
18. Mayberg TS, Lam AM, Matta BF, Domino KB, Winn HR. Ketamine does not increase cerebral blood flow velocity or intracranial pressure during isoflurane/nitrous oxide anesthesia in patients undergoing craniotomy. Anesth Analg. 1995;81:84–9.
19. 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.