European Review for Medical and Pharmacological Sciences 2019; 23: 1807-1815

Effect of different doses of ketamine with low-dose rocuronium on intubation conditions in children: prospective randomized double blind trial

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Abstract. – OBJECTIVE: The effect of ketamine on intubation condition, when used as an induction agent with low-dose rocuronium, is unknown. This study aimed to compare the effects of three doses of ketamine used with 0.3 mg/kg rocuronium and 1 μg/kg fentanyl on intubation conditions in children undergoing short elective surgery.

PATIENTS AND METHODS: The study was performed as a prospective, randomized double-blind clinical trial. A total of 60 children aged 2 to 12 years, who were scheduled for inguinal herniorrhaphy under general anesthesia, were randomly allocated into three groups on the basis of ketamine dose: 1 mg/kg (Group K_1, *n* = 20), 1.5 mg/kg (Group $K_{1.5}$, *n* = 20), and 2 mg/kg (Group K_2, *n* = 20). The primary outcome was the intubation condition. Other assessments included hemodynamic data, recovery profile, adverse events in the postanesthetic care unit (PACU) and use of fentanyl as a rescue analgesic in the PACU were also assessed.

RESULTS: The occurrence of a clinically acceptable intubation condition increased with the use of an increased dose (≥ 1.5 mg/kg) (K_1/$K_{1.5}$/K_2: 30%/65%/65%; *p*=0.038, for trends *p*=0.028). Hemodynamic data, recovery profile and adverse events in PACU showed no difference among groups. Fentanyl dose used in the PACU was higher in K_1 than K_2 and the number of patients requiring rescue analgesics in the PACU decreased in accordance with the dose of ketamine (K_1/$K_{1.5}$/K_2: 30%/15%/0%; *p*=.031, for trends *p*=0.013).

CONCLUSIONS: Different intubation conditions were observed on the basis of ketamine dose used in conjunction with 0.3 mg/kg rocuronium and fentanyl 1 μg/kg. Ketamine dose ≥ 1.5 mg/kg with low-dose rocuronium should be used to improve intubation conditions in pediatrics.

Key Words
Intubation, Pediatric, Rocuronium, Ketamine.

Introduction

Neuromuscular blocking agents are frequently used during general anesthesia to facilitate endotracheal intubation. Rocuronium, a steroidal nondepolarizing agent, is most commonly used for this purpose; rocuronium exhibits a fast onset time and low potency[1]. Administration of rocuronium 0.6 mg/kg (2 × effective dose 95) enables endotracheal intubation within 60 to 90 seconds[2,3], although the duration of action is 24 to 40 minutes[4,5]. There is a need to reduce the dose of neuromuscular blocking agents, particularly for shorter, outpatient surgical procedures; this reduces the duration of action and expedites recovery time. Notably, this reduced dose of rocuronium leads to delayed onset time resulting in inappropriate intubation conditions[6]. Therefore, the selection of the appropriate type and dose of induction agent to improve intubation condition is important in such situations.

Ketamine is a sedative-hypnotic agent that is useful for anesthesia induction, sedation, and analgesia[7-9]. Scholars[10-12] have shown that the application of a subanesthetic dose of ketamine, as an adjuvant agent, results in improved intubation conditions. In addition, the use of ketamine as a sole anesthesia induction agent with 0.6 mg/kg rocuronium has been shown to result in good to excellent intubation conditions compared with other agents[13,14]. These results suggest that ketamine may be useful when used as an induction agent, in combination with low-dose rocuronium during endotracheal intubation. The clinical ketamine induction dose used in routine practice is 1-2 mg/kg[15]. However, the effect of ketamine induction dose on the intubation condition, when used in combination with low-dose rocuronium, is currently unknown. This work aimed to compare the effects of three doses of ketamine, used with 0.3 mg/kg rocuronium and fentanyl 1 μg/kg on intubation conditions in children undergoing short elective surgery.

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Patients and Methods

The study protocols were approved by our Ajou Institutional Review Board (AJIRB-MED-CT4-15-153) and the trial was registered in ClinicalTrials.gov (NCT02646709). We included children aged 2 to 12 years, with an American Society of Anesthesiologists (ASA) physical state of 1 or 2, who were scheduled for elective inguinal herniorrhaphy surgery under general anesthesia with endotracheal intubation. Patients with preoperative upper respiratory infection within 14 days before the scheduled surgery, or patients who were anticipated to exhibit difficult intubation, were excluded. All patients were enrolled after informed consent was obtained from their legal guardians, and additional informed consent was obtained from patients older than 6 years. A total of 60 patients were enrolled, and patients were randomized using a computer-generated random table into three groups according to the ketamine dose: 1 mg/kg (Group K_1), 1.5 mg/kg (Group $K_{1.5}$), and 2 mg/kg (Group K_2). Ketamine (Huons, Seongnam, Korea) was prepared according to the allotted dose by mixing it with normal saline to a total of 5 ml for all groups. All patients entered the operating theater with their respective legal guardians, and routine monitoring was performed. Baseline hemodynamic data were recorded. Induction was begun after administration of the prepared 5-ml ketamine solution, and manual ventilation with 100% oxygen was performed. Fentanyl (1 μg/kg) and rocuronium (0.3 mg/kg) were sequentially administered, and endotracheal intubation was performed 90 seconds after rocuronium administration. After intubation, the cuff was inflated, and end-tidal CO_2 was assessed to determine successful intubation. If the first intubation was not successful, it was judged as "failed intubation", and sevoflurane was administered to induce deep anesthesia for further general anesthesia. All intubations were performed by a single expert with more than 10 years of experience. The primary outcome was assessed by intubation condition, as outlined in the guideline established by the International Consensus Conference[16,17]. The guideline lists 5 parameters including laryngoscopy easiness, vocal cords position, vocal cords movement, tracheal tube insertion and limb movement and coughing during cuff inflation. All parameters were assessed by using 3 grades: excellent, good or poor. A grade of "poor" in any category was defined as a clinically not acceptable intubation condition (Table I). Hemodynamic data were measured 5 times: at baseline, after ketamine injection, after intubation, 5 minutes after intubation, and 10 minutes after intubation. The time from intubation to extubation, postanesthetic care unit (PACU) stay time, and time until the patient condition was suitable for PACU discharge were also recorded. The highest emergence agitation score within 15 minutes after admission to the PACU was recorded using the Watcha scale[18]: 1, calm; 2, crying, but can be

Table I. Evaluation of intubating conditions.

Variable assessed	Clinically acceptable		Not clinically acceptable
	Excellent	Good	Poor
Laryngoscopy	Easy	Fair	Difficult
Vocal cords			
Position	Abducted	Intermediate	Closed
Movement	None	Moving	Closing
Reaction to insertion of tracheal tube and/or cuff inflation			
Movement of the limbs	None	Slight	Vigorous
Coughing	None	Diaphragm	Sustained (>10 s)

Intubation conditions
Excellent; all qualities are excellent.
Good; all qualities are either excellent or good.
Poor; the presence of a single quality listed under poor.
Laryngoscopy
Easy; jaw relaxed, no resistance to blade insertion.
Fair; jaw not fully relaxed, slight resistance to blade insertion.
Difficult; poor jaw relaxation, active resistance of the patient to laryngoscopy.

consoled; 3, crying but cannot be consoled; 4, agitated and thrashing around. Any adverse events in the PACU (e.g., vomiting, bradycardia and desaturation) were recorded. Fentanyl (0.5 ug/kg) was administered when a patient showed signs of pain or at the patient's or parent's request. The fentanyl dose and the number of patients requiring rescue analgesics in the PACU were also recorded. The clinician who performed the intubation and assessed the above parameters was blinded to the patients' group and dose of ketamine, and the researcher who performed the randomization and preparation of ketamine was not involved in any patient assessment.

Sample Size Calculation and Statistical Analysis

According to the results of the pilot study, 40% (4/10) of the patients showed clinically acceptable intubation condition with 1 mg/kg ketamine, 1 μg/kg fentanyl and 0.3 mg/kg rocuronium. Significant improvement in the intubation condition was considered to increase the clinical acceptability to 80%. The number of patients required for each group was determined as n=20, based on a 2-sided test using $\alpha = 0.05$ and $\beta = 0.2$. Statistical analysis was performed using SPSS 23.0 (IBM, Armonk, NY, USA). Data are expressed as the mean ± standard deviation or numbers of patients. Categorical data were analyzed using Pearson's chi-squared test or Fisher's exact probability test where appropriate, followed by Bonferroni adjusted chi-squared or Fisher's exact probability tests. Trends with respect to an increase in the dose of ketamine were studied using the chi-squared test for trends. Continuous data were analyzed using ANOVA, followed by post-hoc Tukey's HSD test. Hemodynamic changes were compared by repeated measures of ANOVA. p-values < 0.05 were considered to be significant.

Results

Sixty-five children were screened and a total of 60 children were randomized into one of the three study groups. A flow diagram of this work is shown in Figure 1. All 60 patients completed this study. Demographic data regarding age, sex, weight, height, American Society of Anesthesiologist (ASA) physical state, operation time and anesthesia time were comparable among the groups (Table II).

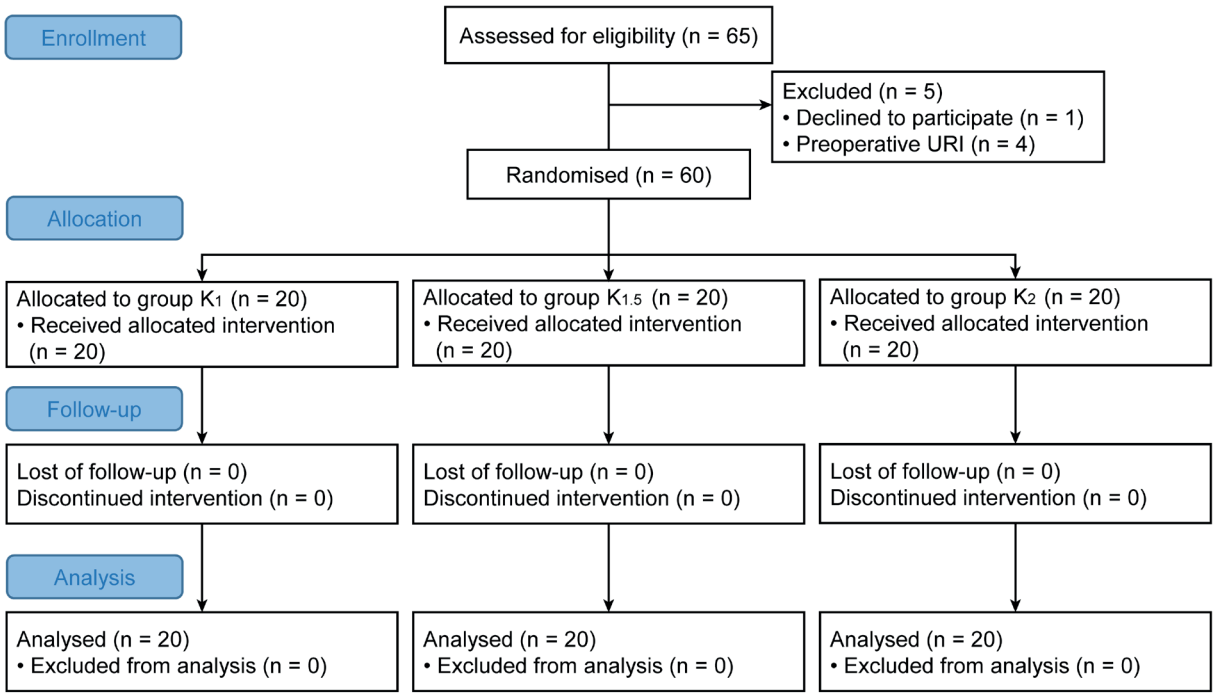

Figure 1. Flow chart. URI, upper respiratory infection. Group K_1; Ketamine dose 1.0 mg/kg. Group $K_{1.5}$; Ketamine dose 1.5 mg/kg. Group K_2; Ketamine dose 2.0 mg/kg.

Table II. Demographic data.

Variables	Group K_1	Group $K_{1.5}$	Group K_2
Sex M:F, n (%)	14:6 (70:30)	13:7 (65:35)	10:10 (50:50)
Age, years	4.4 ± 1.7	5.5 ± 2.7	4.9 ±1.8
Height, cm	104.7 ± 12.9	111.3 ± 18.4	105.7 ± 24.5
Weight, kg	18.3 ± 7.0	20.5 ± 8.3	18.6 ± 5.4
ASA 1/2, n (%)	20/0 (100/0)	19/1 (95/5)	20/0 (100/0)
Operation time, min	26.0 ± 11.8	23.3 ± 17.0	21.0 ± 13.5
Anesthesia time, min	52.1 ± 14.6	48.7 ± 19.4	51.1 ± 17.0

Values are mean ± SD or number (%).
ASA, American Society of Anesthesiologists physical state
Group K_1; Ketamine dose 1.0 mg/kg.
Group $K_{1.5}$; Ketamine dose 1.5 mg/kg.
Group K_2; Ketamine dose 2.0 mg/kg.

Intubation conditions are shown in Table III. Regarding the overall intubation condition, the occurrence of clinically acceptable intubation conditions were 6/20 (30%), 13/20 (65%), and 13/20 (65%) in groups K_1, $K_{1.5}$, and K_2, respectively (p = 0.038). The occurrence of a clinically acceptable intubation condition increased with the dose of ketamine, which was revealed by chi-squared test for trends (p = 0.028). Among variables assessed for the intubation condition, the occurrence of limb movement significantly differed among groups (p = 0.039, chi-squared test for trends = 0.093). Intubation failure occurred in one child in group K_1 due to vocal cord closure during the first attempt. This case was categorized as failed intubation, and the patient subsequently underwent successful intubation after the administration of sevoflurane to increase the depth of anesthesia. In all other children, tracheal intubation was possible even when the intubation condition was clinically unacceptable because the conditions for laryngoscopy as well as vocal cord position and movement were excellent or good. Two variables of intubation condition, limb movement and coughing just after intubation, were critical in determining whether the overall intubation condition was clinically acceptable. Hemodynamic data are shown in Table IV. After ketamine injection, all hemodynamic parameters increased in patients in all three groups, compared with the baseline. After intubation, hemodynamic parameters increased further and then returned to the baseline. However, there were no intergroup differences. Recovery profiles and adverse events are shown in Table V. Extubation time and total PACU stay time were not significantly different between the groups. Adverse events such as vomiting, bradycardia, desaturation and emergence agitation showed no marked differences among groups. The dose of fentanyl used in the PACU was different among groups (p = 0.045). The numbers of patients requiring a rescue analgesic in the PACU were as follows: 6 (30%), 3 (15%), and 0 cases for group K_1, $K_{1.5}$, and K_2, respectively (p = 0.031). The occurrence of fentanyl use increased with the dose of ketamine, as revealed by the chi-squared test for trends (p = 0.013).

Discussion

The current study demonstrated that ketamine at doses of 1.5 and 2 mg/kg combined with 1 μg/kg fentanyl and 0.3 mg/kg rocuronium resulted in improved intubation conditions without delayed recovery compared with ketamine at a dose of 1.0 mg/kg. Hemodynamic changes were similar among all three doses of ketamine. The dose of ketamine, when used as a sole induction agent, is chosen arbitrarily by anesthesiologists in the range of 1 to 2 mg/kg[15]. Our data, however, suggest that when used with low-dose rocuronium, a dose of at least 1.5 mg/kg ketamine should be used to ensure a clinically acceptable intubation condition. Using ketamine doses of 1.5 and 2 mg/kg, conditions for laryngoscopy, as well as vocal cord position and movement, were excellent or good for all children; thus the conditions for the passage of the tracheal tube were excellent or good. Children assessed to be clinically unacceptable in the $K_{1.5}$ and K_2 groups showed sustained cough over 10 seconds without vigorous movement of limbs, with the exception of one child, in whom this cough rapidly disappeared following ventilation with sevoflurane. However, intubation

Table III. Intubation conditions.

Variables	Group K_1	Group $K_{1.5}$	Group K_2	*p*-value
Intubation condition				
Acceptable/Non-acceptable	6/14 (30/70)	13/7 (65/35)	13/7 (65/35)	0.038 0.028[a]
Excellent/Good/Poor	2/4/14 (10/20/70)	7/6/7 (35/30/35)	7/6/7 (35/30/35)	0.129 0.029[a]
Laryngoscopy				
Acceptable/Non-acceptable	20/0 (100/0)	20/0 (100/0)	20/0 (100/0)	>0.999
Easy/Fair/Difficult	18/2/0 (90/10/0)	18/2/0 (90/10/0)	19/1/0 (95/5/0)	>0.999
Vocal cords position				
Acceptable/Non-acceptable	19/1 (95/5)	20/0 (100/0)	20/0 (100/0)	>0.999
Abducted/Intermediate/Closed	18/1/1 (90/5/5)	18/2/0 (90/10/0)	19/1/0 (95/5/0)	>0.999
Vocal cords movement				
Acceptable/Non-acceptable	19/0 (100/0)	20/0 (100/0)	20/0 (100/0)	>0.999
None/Moving/Closing	16/3/0 (84.2/15.8/0)	18/2/0 (90/10/0)	19/1/0 (95/5/0)	0.507
Movement of the limbs				
Acceptable/Non-acceptable	15/4 (78.9/21.1)	20/0 (100/0)	19/1 (95/1)	0.039 0.093[a]
None/Slight/Vigorous	8/7/4 (42.1/36.8/21.1)	12/8/0 (60/40/0)	18/1/1 (90/5/5)	0.003 0.002[a]
Coughing				
Acceptable/Non-acceptable	7/12 (37/63)	13/7 (65/35)	13/7 (65/35)	0.183 0.109[a]
None/Diaphragm/Sustained	4/3/12 (21/16/63)	7/6/7 (35/30/35)	7/6/7 (35/30/35)	0.491 0.138[a]

Values are number (%).
Group K_1; Ketamine dose 1.0 mg/kg.
Group $K_{1.5}$; Ketamine dose 1.5 mg/kg.
Group K_2; Ketamine dose 2.0 mg/kg.
[a]Chi-squared test for trends.

failure occurred in one child with ketamine dose of 1 mg/kg due to vocal cord closure. Vigorous movement of limbs and sustained cough was also more frequently observed in patients who received ketamine at a dose of 1 mg/kg. Thus, the effect of ketamine on the intubation condition, which has been reported in studies with various designs, showed a dose-dependent trend in this study. As an adjuvant agent, the addition of low-dose of ketamine (0.5 mg/kg) to propofol-rocuronium, propofol-remifentanil-cisatracurium, and propofol-remifentanil without a neuromuscular blocking agent was shown to improve intubation condition[10,12,19]. As an induction agent, ketamine provided similar or better intubation conditions compared with etomidate or thiopentone[13,20,21]. The exact mechanism underlying the improved intubation condition resulting from the use of ketamine is unclear. Some studies[10,22] have suggested that ketamine may increase cardiac output, resulting in increased muscle blood flow, and accelerating the onset time of the effect of neuromuscular blocking agents. In contrast, even without a neuromuscular blocking agent and hemodynamic changes, the addition of ketamine has been reported to improve the intubation conditions[19]. In the current work, hemodynamic data, albeit without direct cardiac output measurement, were not different between groups despite the difference in the resultant intubating conditions. Therefore, differences among groups may primarily be attributed to other mechanisms. Among the variables assessed regarding intubation condition in the present study, limb

Table IV. Hemodynamic data.

Variables	Group K_1	Group $K_{1.5}$	Group K_2	*p* -value
MBP, mmHg				0.622
Base	76.8 ± 11.5	79.4 ± 6.2	76.3 ± 10.7	0.591
After induction	101.6 ± 11.7	103.2 ± 14.0	108.7 ± 12.3	0.196
After intubation	120.0 ± 14.5	117.9 ± 18.7	118.0 ± 18.5	0.907
5 min	66.7 ± 11.5	70.6 ± 17.8	73.7 ± 9.7	0.264
10 min	76.6 ± 12.2	79.4 ± 13.8	83.7 ± 10.8	0.191
HR, bpm				0.788
Base	101.8 ± 23.5	101.0 ± 20.0	98.2 ± 20.5	0.868
After induction	110.4 ± 18.2	106.3 ± 16.7	107.0 ± 18.6	0.742
After intubation	120.0 ± 14.5	117.9 ± 18.7	118.0 ± 18.5	0.907
5 min	66.7 ± 11.5	70.6 ± 17.8	73.7 ± 9.7	0.264
10 min	109.0 ± 15.3	105.3 ± 17.0	105.2 ± 15.8	0.681

Values are mean ± SD.
MBP, mean arterial pressure; HR, heart rate.
Group K_1; Ketamine dose 1.0 mg/kg.
Group $K_{1.5}$; Ketamine dose 1.5 mg/kg.
Group K_2; Ketamine dose 2.0 mg/kg.
[a]Chi-squared test for trends.

movement tended to decrease as ketamine dose increased, indicating that increased depth of anesthesia might have prevented limb movement response to a strong stimulus intubation[19]. Cough also tended to decrease with increased ketamine dose. The suppression of N-methyl-D-aspartate (NMDA) receptors by ketamine could have mitigated the occurrence and severity of coughing after intubation because cough is evoked by the involvement of NMDA receptors, and the blockade of NMDA receptors by ketamine is dose-dependent[23-25]. Previous studies[26-29] using low-dose rocuronium (0.15 to 0.3 mg/kg) mostly utilized propofol or other volatile agents as the main induction agents in children. Various adjuvant agents have been used in combination, including remifentanil, alfentanil, low-dose ketamine and nitrous oxide. The reported occurrence of a clinically acceptable intubation condition have been 65 % to 100%; in the current study, this

Table V. Recovery profile.

Variables	Group K_1	Group $K_{1.5}$	Group K_2	*p* -value
Extubation time, min	11.1 ± 3.4	10.0 ± 2.5	13.2 ± 5.3	0.062
Time to condition to discharge, min	19.4 ± 8.6	21.7 ± 8.5	24.0 ± 10.1	0.286
PACU stay, min	40.0 ± 7.9	40.4 ± 7.1	39.7 ± 4.9	0.958
Vomit, n (%)	3 (15)	2 (10)	2 (10)	>0.999
Bradycardia, n (%)	0 (0)	1 (5.3)	0 (0)	0.322
Desaturation, n (%)	0 (0)	1 (5.3)	0 (0)	0.322
Agitation 1/2/3/4, n (%)	11/5/2/2 (55/25/10/10)	15/5/0/0 (75/25/0/0)	12/5/1/2 (60/25/5/10)	0.625
Fentanyl, n (%)	6 (30)	3 (15)	0 (0)	0.031 0.013[a]
Fentanyl, ug/kg	0 [0–0.5]	0 [0–0]	0 [0–0]	0.045

Values are mean ± SD, number (%) or median [interquartile range].
PACU, postanesthetic care unit.
Group K_1; Ketamine dose 1.0 mg/kg.
Group $K_{1.5}$; Ketamine dose 1.5 mg/kg.
Group K_2; Ketamine dose 2.0 mg/kg.
[a]Chi-squared test for trends.

occurrence was 65% with ketamine doses of 1.5 and 2 mg/kg, which is the lower margin of the reported range. We consider this occurrence to be clinically unsatisfactory because cough after intubation can damage the airway mucosa causing in postoperative edema, stridor, croup and airway obstruction in children with a small airway[29]. Several factors in this work design may have influenced this outcome, including the sequence and timing of drug administration. The onset time of fentanyl is approximately 2-3 minutes[30], whereas the onset time of ketamine is 30-40 seconds[31]. Fentanyl should theoretically be given first to achieve full clinical effectiveness; however, ketamine was given prior to fentanyl, as preoxygenation is difficult to achieve in children and because of the risk of occurrence of chest wall rigidity due to fentanyl. Thus, the administration of ketamine prior to fentanyl may have resulted in a short period of time available to achieve the maximum effect of fentanyl. Early administration of fentanyl or administration of fast-acting alfentanil may further improve intubation conditions. Alternatively, if intubation rocuronium administration is delayed slightly, the occurrence of a clinically acceptable intubation condition may increase. Further studies are needed to determine a better combination of induction agents, the respective doses and injection timing with low-dose rocuronium for various clinical applications. There were no differences among groups in recovery profiles and adverse events, with the exception of the use of fentanyl in the PACU, which decreased with an increase in the dose of ketamine. The analgesic effect of ketamine is known to reduce postoperative pain intensity and analgesic requirement[32,33]. Specifically, the use of ketamine results in preemptive analgesia, such that the administration of ketamine before a noxious stimulus is more effective than administration after the noxious stimulus is applied[34-36]. However, conflicting results have been reported with regard to the dose-dependent pattern of preemptive analgesia. Aqil et al[37] showed a ketamine dose-related reduction in analgesic use and prolongation of the time to the first analgesia request. Laskowski et al[38] reported that this phenomenon was not related to the dose or time of administration of ketamine. Our findings support the hypothesis that preemptive analgesia shows a dose-dependent pattern. One of the limitations of this study was the elevated hemodynamic response to tracheal intubation. Mean blood pressures after ketamine injection and after intubation were increased by more than 30%, compared with the baseline value. Heart rate after intubation was increased by more than 20%, compared with the baseline value. These effects are more harmful to vulnerable patients. Further researches are needed regarding the dose and timing of agents that may reduce the hemodynamic stimulatory effects of ketamine.

Conclusions

We found that the induction dose of ketamine showed a differential effect on intubation condition in pediatric patients, when combined with 1 μg/kg fentanyl and 0.3 mg/kg rocuronium. A $\geq$ 1.5 mg/kg ketamine improved overall intubation conditions in children, compared with a dose of 1 mg/kg ketamine.

Acknowledgments

We would like to thank Editage (www.editage.co.kr) for English language editing. Clinical trial registration No.: NCT02646709 (ClinicalTrials.gov).

Conflict of Interests

The authors declare that they have no conflict of interest.

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