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Remifentanil requirement for acceptable intubation conditions with two different doses of ketamine without a neuromuscular blocking agent in pediatric patients

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Abstract. – OBJECTIVE: The optimal remifentanil concentration for improving intubation conditions when intubation is performed without neuromuscular blocking agents (NMBAs) but with ketamine as an induction agent remains unknown. Here, we aimed to identify the effective bolus doses of remifentanil required to achieve acceptable intubation conditions upon anesthesia induction with 1 or 2 mg/kg ketamine without NMBAs.

PATIENTS AND METHODS: In this prospective, double-blinded, randomized up-down sequential allocation study, we enrolled pediatric patients aged 3-12 years undergoing general anesthesia for inguinal hernia surgery. The patients were randomly allocated to one of two groups to receive either ketamine 1.0 mg/kg (K1 group) or 2.0 mg/kg (K2 group) intravenously until seven success-failure pairs were achieved. The remifentanil dose for each patient was determined using the modified Dixon's up-and-down method with an initial dose of 2.5 μg/kg and a step size of 0.5 μg/kg.

RESULTS: In total, 51 patients (22 in the K1 group and 29 in the K2 group) were enrolled. The effective dose (ED)50s of remifentanil for obtaining clinically acceptable intubation conditions under anesthesia induction with ketamine but without NMBAs was 3.2 μg/kg in the K1 group and 1.6 μg/kg in the K2 group. High-dose remifentanil with 1 mg/kg ketamine was associated with more severe chest wall rigidity and lower mean blood pressure and heart rate than was low-dose remifentanil with 2 mg/kg ketamine.

CONCLUSIONS: The ED50 of remifentanil required for clinically acceptable intubation conditions with anesthesia induction using 1 mg/kg ketamine without NMBAs in pediatric patients was twice that when using 2 mg/kg ketamine. The combination of 2 mg/kg ketamine and remifentanil was better at preventing chest wall rigidity.

Key Words:
Intubation, Pediatric, Ketamine, Remifentanil.

Introduction

As the number of patients undergoing outpatient surgery increases, various efforts are being made to reduce the postoperative recovery time and the length of hospital stay. Accordingly, several studies[1-11] have investigated the induction and maintenance of anesthesia without using neuromuscular blocking agents (NMBAs) for safe same-day discharge without the residual effects of NMBAs. To date, many studies[3,4,9,12,12] have reported the use of thiopental, propofol, or sevoflurane as an induction agent in combination with opioids[3,4], sympatholytic drugs[12,13], or local anesthetics[4,9].

Ketamine, an induction agent commonly used in pediatric anesthesia, offers greater improvement of the intubation condition than do other induction agents[14,15]. Remifentanil, which is used as an anesthetic supplement, also improves the intubation condition[3,11] and offers advantages, such as rapid onset and short duration of anesthesia owing to its rapid degradation by plasma or tissue esterase. However, the appropriate remifentanil concentration required to improve intubation conditions when ketamine is used as an induction agent remains unknown.

In general, the induction dose of ketamine is 1-2 mg/kg, and this dose is arbitrarily selected in clinical practice. Depending on the ketamine

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dose, the remifentanil dose used to improve the intubation condition may also vary. Therefore, this study was designed to identify effective bolus doses of remifentanil for an acceptable intubation condition without NMBAs when anesthesia was induced with 1 or 2 mg/kg ketamine.

Patients and Methods

Patients and Randomization

This prospective, double-blinded, randomized up-down sequential allocation study was conducted at the Ajou University Hospital (Suwon, South Korea) between December 2015 and November 2018. This study was approved by the Institutional Review Board of Ajou University Hospital (AJIRB-MED-DRU-15-354) and was registered at ClinicalTrials.gov (NCT No: 02655380). Written informed consent for inclusion was obtained from the parents of all children enrolled in the study.

Pediatric patients aged 3-12 years with an American Society of Anesthesiologists physical status of I or II who underwent general anesthesia for inguinal hernia surgery were enrolled in this study. Patients with a history of upper respiratory tract infection within 14 days or those with anticipated difficult intubation were excluded.

Using computer-generated random numbers, the patients were randomly allocated to one of two groups to receive either ketamine 1.0 mg/kg or 2.0 mg/kg intravenously until seven success-failure pairs were achieved. The ketamine solution was prepared using a mixture of ketamine 1.0 mg/kg or 2.0 mg/kg and normal saline to achieve a total volume of 5 mL. The patients, anesthesia providers, and investigators who assessed the intubation conditions were blinded to the treatment groups. An independent researcher prepared the solutions and randomly allocated the patients to the two groups.

Assessments

All patients were escorted by their parents into the operating room and were monitored using electrocardiography, pulse oximetry, noninvasive arterial blood pressure monitoring, and capnography. Either 1 mg/kg or 2 mg/kg ketamine was rapidly injected intravenously to induce anesthesia. After confirming loss of consciousness, the patients were manually ventilated with 100% oxygen, and remifentanil was gradually injected over a period of 60 s. Sixty seconds after remifentanil injection, the trachea was intubated with a cuffed tracheal tube. The scores for the ease of manual ventilation, which can be affected by chest wall rigidity induced by remifentanil, were as follows: 1) able to ventilate under a peak airway pressure of $\leq$20 cmH_2O; 2) able to ventilate above peak airway pressure of 20 cmH_2O; and 3) difficult facemask ventilation. All intubations were performed and assessed by an experienced anesthesiologist. The intubation conditions were evaluated using a score described by Viby-Mogensen et al[16], which included the ease of laryngoscopy, vocal cord position and movement, and patient movement and coughing after the insertion of the tracheal tube and/or cuff inflation. The intubation condition was considered clinically acceptable when all variables were assessed as excellent or good. After the trachea was intubated, the tracheal tube cuff was slowly inflated, and successful intubation was confirmed *via* auscultation and capnography. If the first intubation attempt failed, a second attempt was performed after either deepening the anesthesia with sevoflurane or administering an NMBA at the anesthesiologist's discretion; moreover, the attempt was recorded as failed intubation regardless of the intubation condition.

The remifentanil dose in each patient was determined using the modified Dixon's up-and-down method with 0.5 μg/kg as the step size. The initial remifentanil dose was started at 2.5 μg/kg. If intubation was successful, the remifentanil dose for the next patient was reduced by 0.5 μg/kg, and if intubation failed, the dose was increased by 0.5 μg/kg. Hemodynamic parameters, including the mean blood pressure (MBP) and heart rate (HR), were recorded immediately before anesthesia induction (baseline), after remifentanil administration (before intubation), immediately after intubation, and 5 and 10 min after intubation.

Statistical Analysis

The sample size was based on the modified Dixon's up-and-down method[17], in which a minimum of seven crossover points in each group was required to estimate the effective dose (ED)50. Patients were recruited to achieve seven success-failure pairs in each group. ED50 was defined as the mean of the crossover doses. The data were also subjected to isotonic regression with the pooled-adjacent-violators algorithm (PAVA) and the bootstrap method to estimate the ED50 and ED95 of remifentanil with confidence intervals (CIs). SPSS for Windows/Macintosh, Version 11.0 (SPSS Inc., Chicago, IL, USA) was utilized to compare the two groups. Independent

t-test, Mann-Whitney U statistic, chi-square test, or Fisher's exact test were used, where appropriate, for the analyses. Hemodynamic changes were compared using repeated-measures analysis of variance (ANOVA). Statistical significance was set at $p<0.05$.

Results

In total, 51 pediatric patients completed the study (Figure 1). Among them, 22 and 29 patients were enrolled in the K1 and K2 groups, respectively, until seven success-failure pairs were included. The patient characteristics are presented in Table I. No significant difference was observed between the groups with respect to age, weight, height, and the American Society of Anesthesiologists physical status.

The sequence of clinically acceptable intubation conditions is presented in Figure 2. The estimated ED50 of remifentanil was significantly different between the K1 and K2 groups (3.2±0.3 *vs.* 1.6±0.5 μg/kg, $p<0.001$). From isotonic regression with PAVA and the bootstrap method, the ED50s were 3.0 (83% CI: 2.8-3.3) and 1.2 (83% CI: 0.7-1.6) in the K1 and K2 groups, respectively, and the ED95s were 3.9 (95% CI: 3.5-4.0) and 2.4 (95% CI: 1.5-2.5) in the K1 and K2 groups, respectively (Figure 3). The CIs of the ED50 and ED95 data did not overlap, i.e., they were significantly different between the groups.

The intubation data are presented in Table II and did not differ between the groups. The ease of manual ventilation, as determined by remifentanil-induced chest wall rigidity, was significantly different between the groups ($p<0.001$). The number of patients with a score of 1/2/3 for ease of manual ventilation was 7/6/9 in the K1 group and 20/9/0 in the K2 group. In nine patients in the K1 group in whom face-mask ventilation was difficult, the range of remifentanil dose was 2.5-3.5 μg/kg, and seven of these patients were in clinically unacceptable intubation conditions. A decrease in oxygen saturation to <94% was observed in only two patients (73% and 83%), and both had severe chest wall rigidity.

Table I. Patient characteristics.

Variable	K1 Group (n=22)	K2 Group (n=29)	*p*-value
Age (years)	5.4±2.1	6.1±1.8	0.190
Sex (male/female)	11/11	13/16	0.782
Weight (kg)	20.1±6.7	21.0±6.0	0.614
Height (cm)	111.3±15.3	111.0±21.5	0.956
ASA PS (I/II)	21/1	28/1	0.682

Data are presented as mean±standard deviation or as numbers. K1 Group: ketamine 1 mg/kg as an induction agent; K2 Group: ketamine 2 mg/kg as an induction agent. ASA PS: American Society of Anesthesiologists physical status.

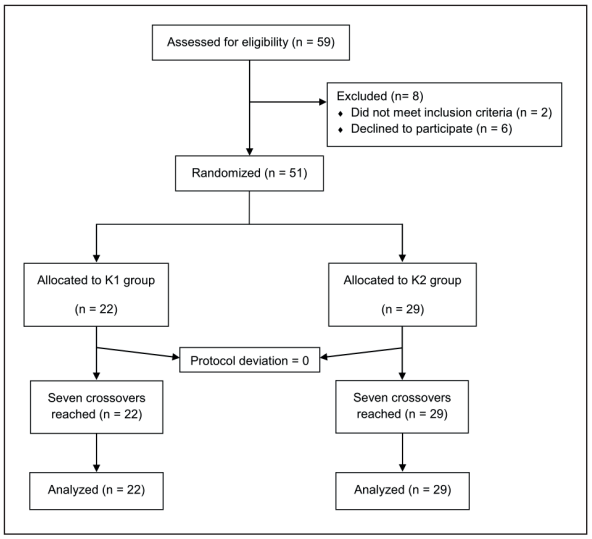

Figure 1. Flow diagram of the study.

Hemodynamic changes are presented in Figure 4. Both MBP and HR showed significant differences between the two groups according to repeated-measures ANOVA (group effects, $p<0.001$). In addition, MAP and HR showed significant changes with time ($p<0.001$) and significant interaction with time × group ($p = 0.004$ and 0.032, respectively) in the K1 and K2 groups. Overall, the mean of these data was higher in the K2 group than in the K1 group. MBP was significantly higher after remifentanil administration (before intubation), immediately after intubation, and 5 min after intubation in the K2 group than in the K1 group. Similarly, HR was significantly higher after remifentanil administration (before intubation) and immediately after intubation in the K2 group than in the K1 group.

Discussion

In this study, we aimed to identify the effective bolus dose of remifentanil for an acceptable intu-

Table II. Intubation data (response to intubation).

Variable	K1 Group (n = 22)	K2 Group (n = 29)	*p*-value
Clinically acceptable intubation condition (acceptable/unacceptable)	11/11	16/13	0.714
Laryngoscopy (excellent/good/poor)	9/13/0	20/8/1	0.043
Vocal cord			
Position (abducted/intermediate/closed)	2/12/8	10/14/4	0.052
Movement (none/moving/closing)	11/5/6	20/4/4	0.314
Reaction to the insertion of the tracheal tube and/or cuff inflation			
Movement of the limbs (none/slight/vigorous)	9/7/1	18/7/0	0.247
Coughing (none/diaphragm/sustained >10 s)	10/5/2	12/5/8	0.237

Data are represented as numbers. K1 Group: ketamine 1 mg/kg as an induction agent; K2 Group: ketamine 2 mg/kg as an induction agent

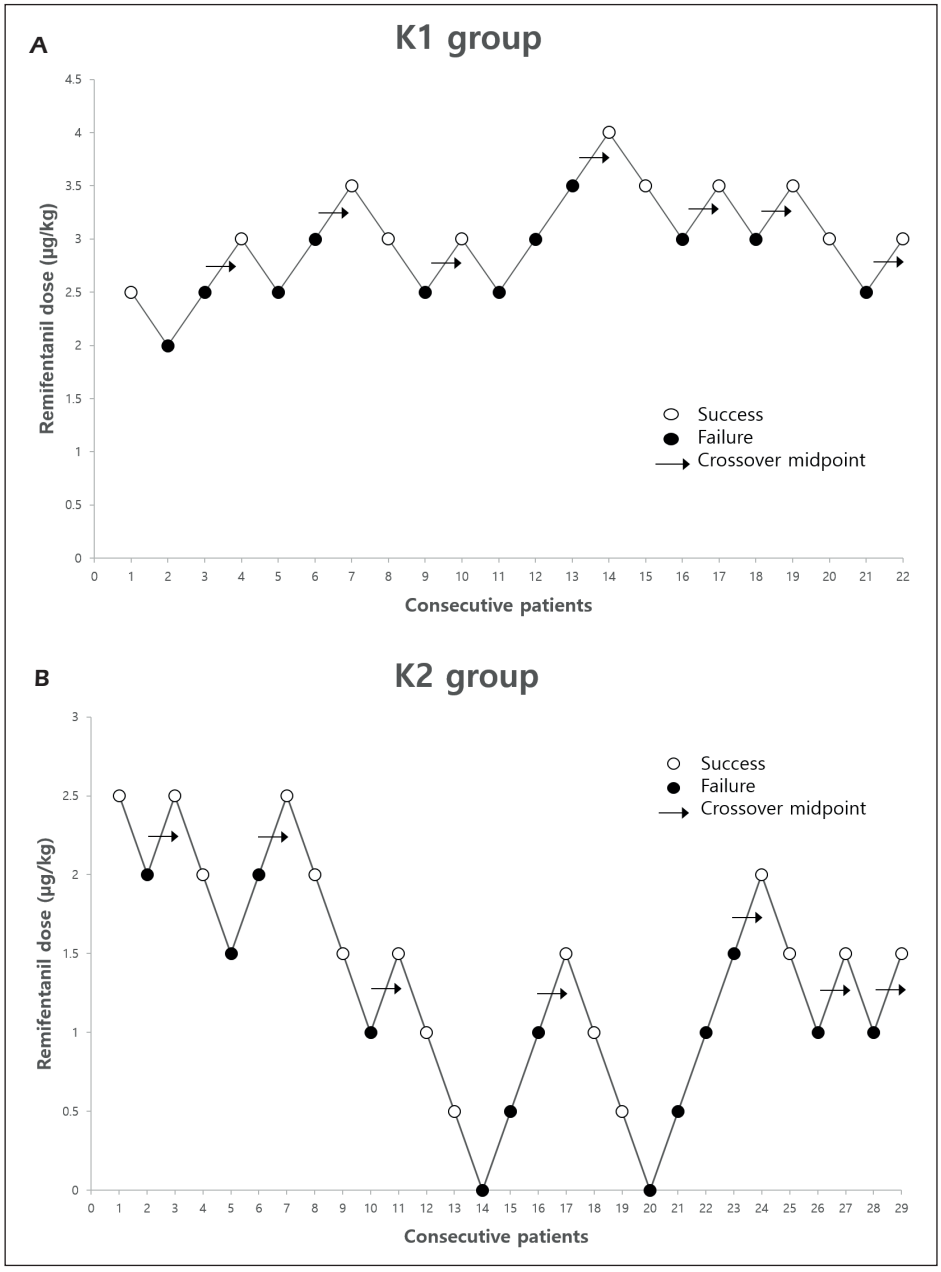

Figure 2. Intubation conditions at different ketamine doses. Arrows indicate the midpoint of the remifentanil dose of all independent pairs of patients involving crossover from the clinically unacceptable to acceptable condition of intubation. **A,** Intubation condition with ketamine 1 mg/kg. The remifentanil dose for clinically acceptable intubation in 50% of the patients is 3.2±0.3 μg/kg. **B,** Intubation condition with ketamine 2 mg/kg. The remifentanil dose for clinically acceptable intubation in 50% of the patients is 1.6±0.5 μg/kg.

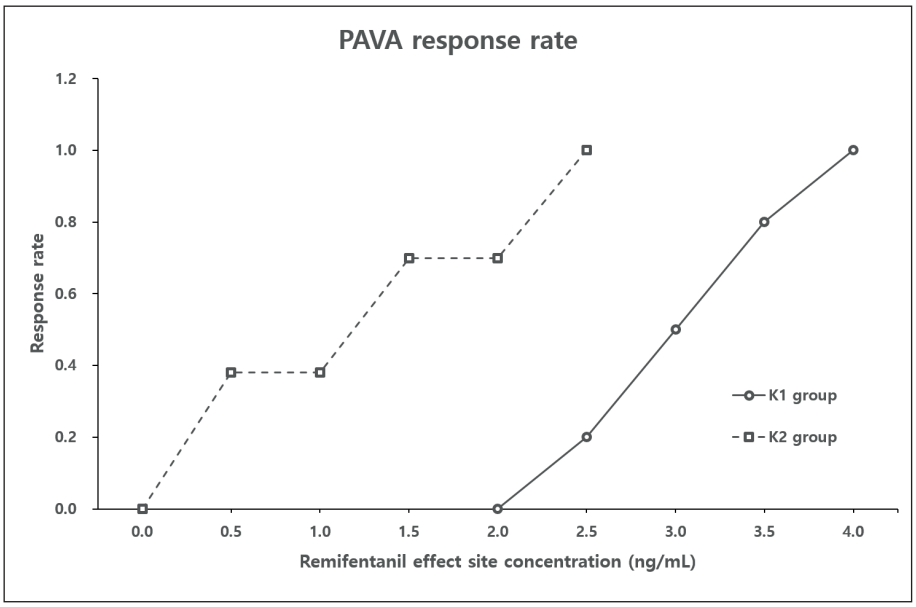

Figure 3. The pooled-adjacent-violators algorithm response rate of remifentanil dose and reaction to intubation. The remifentanil dose with ketamine 1 mg/kg at which there is a 50% and 95% probability of clinically acceptable intubation is 3.0 μg/kg and 3.9 μg/kg, respectively (K1 group). Moreover, the remifentanil dose with ketamine 2 mg/kg at which there is a 50% and 95% probability of clinically acceptable intubation condition is 1.2 μg/kg and 2.4 μg/kg, respectively (K2 group). PAVA, pooled-adjacent-violators algorithm.

bation condition without NMBAs when anesthesia was induced with 1 or 2 mg/kg ketamine. We found that the ED50s of remifentanil required for obtaining a clinically acceptable intubation condition under anesthesia induction with ketamine without NMBAs in pediatric patients were 3.2 μg/kg in the K1 group and 1.6 μg/kg in the K2 group. High-dose remifentanil with 1 mg/kg ketamine was associated with more severe chest wall rigidity and lower MBP and HR than was low-dose remifentanil with 2 mg/kg ketamine.

For tracheal intubation without the use of NMBAs, various combinations of induction drugs, such as sevoflurane, propofol, and thiopental, and adjuvant drugs, such as opioids and lidocaine, have been reported[18-20]. Remifentanil offers advantages, such as rapid onset of anesthesia and a fast elimination half-life of 3.4-5.7 min in children, which are similar to those in adults[21]; therefore, its effects have been investigated in combination with thiopental, propofol, and etomidate[22,23]. The combination with propofol was reported to yield better results than the combination with thiopental and etomidate, but clinically high doses of both propofol (≥4 mg/kg) and remifentanil (≥4 μg/kg) would be needed[24], which would put the patient at risk of bradycardia and hypotension[19]. In this study, the effects of the combination of ketamine and remifentanil were investigated. This is because ketamine is known to improve intubation conditions[14,15,17] and its sympathomimetic effect could offset the cardiovascular effect of remifentanil, thereby improving hemodynamic stability[25]. The ED50s of remifentanil were 3.2 and 1.6 μg/kg and the expected ED95s of remifentanil were 3.9 (95% CI: 3.5-4.0) and 2.4 (95% CI: 1.5-2.5) μg/kg in the K1 and K2 groups, respectively. The K1 group (1 mg/kg ketamine) still required a high dose of remifentanil and showed a slightly lower MBP and HR than the baseline values, whereas the K2 group (2 mg/kg ketamine) required half the dose of remifentanil and showed a slightly higher or similar MBP and HR than the baseline values. This suggests that the combination of appropriate doses of ketamine and remifentanil would result in acceptable intubation conditions and stable hemodynamics within the clinical ranges for both drugs.

Remifentanil may induce chest wall rigidity in association with high doses and rapid administration[26,27]. This can make manual face-mask ventilation difficult during anesthesia induction. In this study, remifentanil was injected over a period of 60 s to avoid chest wall rigidity. However, chest wall rigidity was encountered more frequently with remifentanil in our study than in previous studies

while the patients were awake[20,26-30]. Of the 51 patients, nine (17.6%) had difficulty in face-mask ventilation, and all of these patients belonged to the K1 group. Although face-mask ventilation was judged to be difficult in these patients, no change in oxygen saturation was observed; therefore, intubation was attempted 60 s after remifentanil administration according to the protocol. Intubation failed on the first attempt in two of these patients, and rocuronium was used for the second attempt. The intubation condition was finally evaluated as unacceptable in eight patients and good in one patient. The remifentanil doses used for these nine patients ranged from 2.5 to 3.5 μg/kg. In addition to these nine patients with chest wall rigidity, 15 (29.4%; six in the K1 group and nine in the K2 group) required a peak airway pressure of ≥20 cmH_2O for face-mask ventilation. The reason for the high incidence of chest wall rigidity in this study remains unclear. Previous studies[31-33] on rats demonstrated that fentanyl-induced muscle

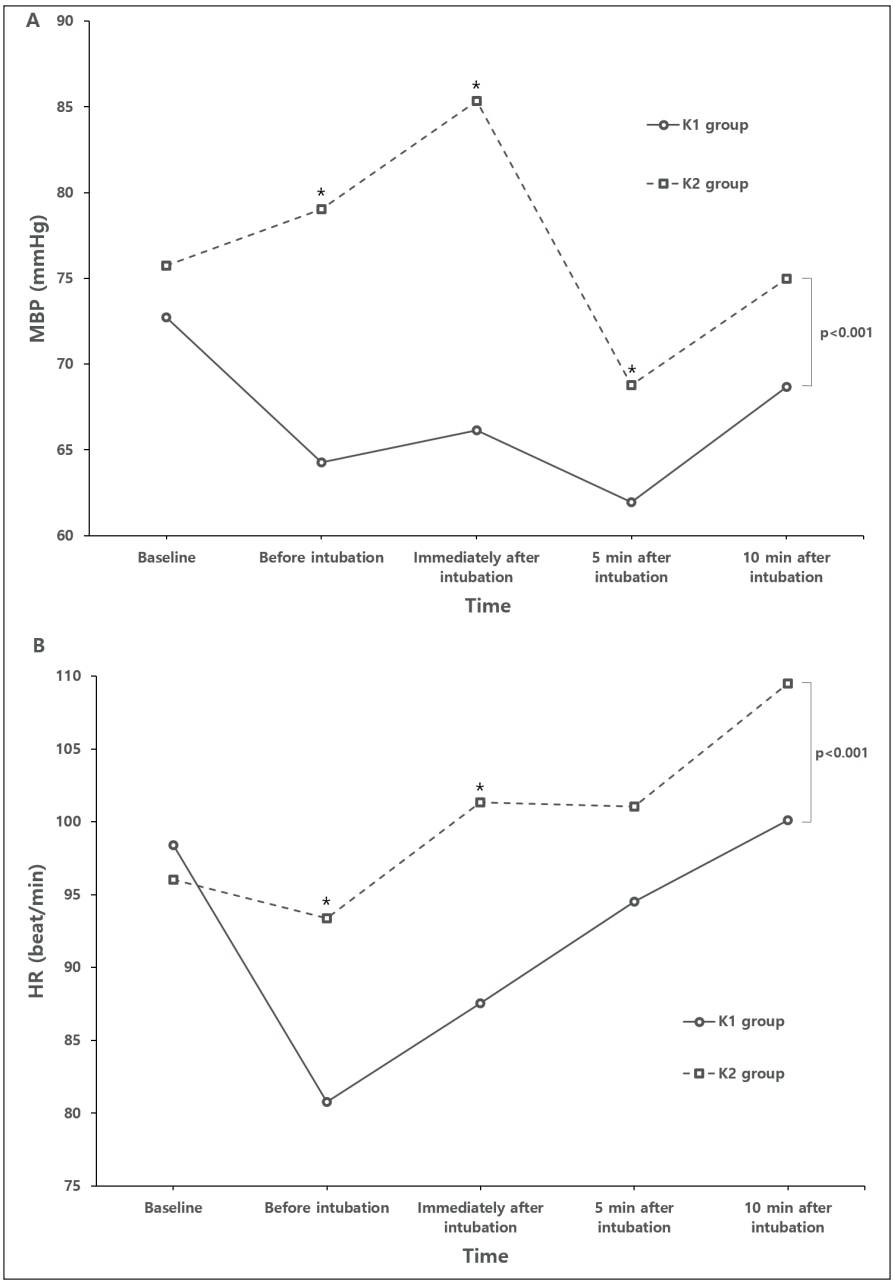

Figure 4. Mean blood pressure and heart rate variations. (**A**) Mean blood pressure (MBP) and (**B**) heart rate (HR) variations in the two groups. Values are expressed as means. *p<0.05 between the two groups at the same time point.

rigidity occurred in both unanesthetized and ketamine-anesthetized rats but not in thiopental-anesthetized rats. Therefore, we suggest that the high incidence of chest wall rigidity could be attributed to the properties of ketamine. Nevertheless, further studies are needed to gain a better understanding of this issue. In this regard, the combination of ketamine and remifentanil requires attention. The data from this study indicate that the combination of 2 mg/kg ketamine with a low dose of remifentanil (0-2.5 μg/kg) is better than the combination of 1 mg/kg ketamine and a higher dose of remifentanil in terms of preventing chest wall rigidity.

This study had some limitations. First, we used a clinically acceptable/unacceptable intubation condition as a binary response for the sequential design of this study, with both "excellent" and "good" being considered an acceptable condition and "poor" being considered an unacceptable condition. If excellent intubation conditions were used as a binary response, the ED50 would have been higher; therefore, this should be considered when referring to the dose results. Second, the remifentanil dosage was based on the total body weight. Studies on opioid dosing recommend using the ideal body weight because patients with obesity are likely to receive an excessive dose of remifentanil. However, in this study, none of the patients had a body mass index of >25 (maximum of 21); thus, the total body weight-based dosing implemented in this study was unlikely to deviate significantly from ideal body weight-based dosing.

Conclusions

The ED50 of remifentanil required for obtaining clinically acceptable intubation conditions under anesthesia induction with 1 mg/kg ketamine without NMBAs in pediatric patients was twice that required with 2 mg/kg ketamine. The combination of ketamine and remifentanil provides acceptable intubation without NMBAs in pediatric patients, and their doses were complementary. However, the combination of high-dose (2 mg/kg) ketamine and remifentanil would be appropriate in clinical practice because of the high incidence of chest wall rigidity observed with the combination of low-dose ketamine and remifentanil.

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Conflicts of Interest
The authors declare no conflicts of interest.

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