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Factors Associated with the Underuse of Sedatives and Neuromuscular Blocking Agents for Pediatric Emergency Endotracheal Intubation in Korea

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Purpose: Rapid sequence intubation (RSI) using sedatives and neuromuscular blocking agents (NMBAs) is recommended for pediatric emergency endotracheal intubation (ETI), but is not frequently performed in Korea. This study aimed to verify factors associated with the underuse of RSI medications.

Materials and Methods: This multicenter retrospective study reviewed patients aged under 18 years who underwent an ETI within 24 hours of arrival at the emergency department between 2016 and 2019. Any cases of ETI during cardiopulmonary resuscitation were excluded. We investigated the characteristics of the patients, intubators, RSI medications, and outcomes. The study cases were classified into no-medication, sedative-only, and sedative-with-NMBA groups. Multivariable logistic regression analysis of RSI medication use was conducted.

Results: A total of 334 cases with a median age of 3.4 years were included in this study. Sedatives and NMBAs were used in 63.8% and 32.9%, respectively. In comparing the no-medication (n=121), sedative-only (n=103), and sedative-with-NMBA (n=110) groups, patient age (median; 1.0 year vs. 2.8 years vs. 11.3 years; $p<0.001$), underlying medical conditions (77.7% vs. 56.3% vs. 36.4%; $p<0.001$), and pediatricians as intubators (76.9% vs. 54.4% vs. 17.3%; $p<0.001$) were different. The factors that influenced sedatives with NMBA use were patient age [for a year increment; adjusted odds ratio (aOR), 1.182; 95% confidence interval (CI), 1.120–1.249], no underlying medical conditions (aOR, 2.109; 95% CI, 1.093–4.070), and intubators other than pediatricians (aOR, 5.123; 95% CI, 2.257–11.626).

Conclusion: RSI accounted for 32.9% of pediatric emergency ETI in Korea. The underuse of RSI medications is associated with younger patient age, underlying medical conditions, and pediatricians as intubators.

Key Words: Hypnotics and sedatives, intubation, neuromuscular blocking agents, pediatrics, rapid sequence induction and intubation

INTRODUCTION

Rapid sequence intubation (RSI) is widely accepted as an optimal method for pediatric emergency endotracheal intubation (ETI).[1] An essential component of RSI is the sequential administration of sedatives and neuromuscular blocking agents (NMBAs), eliminating resistance to direct laryngoscopy and preventing bag-mask-ventilation-induced aspiration gastric contents.[2,3] This process can be helpful in non-fasted infants or young children who are prone to gastric distention due to feeding and crying.[2] The Pediatric Emergency Medicine Com-

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mittee of the American College of Emergency Physicians has recommended using RSI to facilitate successful and safe ETI.[3] Also, several studies have now reported that RSI results in a higher success rate and a lower incidence of adverse events when conducting ETI.[4-6] No absolute contraindications to RSI have been documented, and it is a generally recommended form of intubation other than in patients in cardiac arrest or a deep state of unconsciousness.[3,7]

It is notable that the frequency of sedative and NMBA use for pediatric ETI seems to vary depending on the medical practices of countries in question.[7-11] For example, it is used infrequently in Korea compared to the United States.[5,12] A previous observational study of 1053 pediatric ETI cases in 10 emergency departments (EDs) in the U.S. from 2002 to 2012, using the National Emergency Airway Registry (NEAR) data, reported that 81% of patients received sedatives and NMBAs compared to 16% who had no medication and 3% who received sedatives only.[5] In comparison, a 13-ED-registry study in Korea examining pediatric ETI cases from 2006 to 2010 showed that a mere 12% of these children received sedatives and NMBAs, 68% had no medications, and 20% received sedatives only.[12] The reasons for this underuse of sedatives and NMBAs among pediatric patients eligible for RSI in Korea have not been thoroughly studied.

In the current study, we investigated the characteristics of patients, intubators (clinicians who attempt the initial ETI), RSI medications, and outcomes in a Korean pediatric emergency ETI cohort and verified the factors associated with the underuse of RSI medications in Korea.

MATERIALS AND METHODS

Study design and setting

This multicenter, retrospective observational study reviewed the electronic medical records of pediatric emergency ETI cases that were treated between January 2016 and December 2019 at one of four university-affiliated teaching hospitals in Korea. Each participating hospital had a dedicated pediatric ED with annual visits of 25000–40000 children. ETI was performed by attending physicians or residents, among whom the specialties varied from pediatrics, emergency medicine, and surgery, among others. Pediatric emergency medicine physicians were categorized according to their original specialty (pediatrics or emergency medicine), as the subspecialized boards were not accredited in Korea during the study periods. No standard shared protocol for ETI, such as RSI medication use, existed among the participating hospitals.

Study population

Patients under 18 years of age who had received emergency ETI were initially searched in the institutional databases. Emergency ETI was defined as the receipt of this procedure outside an operating room within 24 hours of the patient's presentation at the ED [but also including cases treated in intensive care units (ICUs), wards, and others]. We did not limit the definition of an emergency ETI to an ED since some patients can be transferred directly to an ICU and then receive this intervention. After our initial screening for pediatric ETI cases, we excluded patients with insufficient medical information, as well as those who were receiving ETI at another hospital, ETI during cardiopulmonary resuscitation, and NMBAs without sedatives. We performed case-based instead of patient-based analyses; that is, each emergency ETI in the same patient during different visits was regarded as a separate case, starting from the first ETI within 24 hours of ED arrival.

Data collection

All relevant medical records, including vital signs, medication administration, nursing records, and clinician procedure notes, were reviewed. A standardized data collection form with the following categories was used in each case: patient (age, sex, weight, underlying medical conditions, and reasons for ETI), intubator (door-to-successful ETI time, ETI-performed place, and intubator's specialty and professional status), RSI medications (sedatives and NMBAs), and outcomes (number of attempts at a successful ETI, physiologic adverse events, ventilator days, and in-hospital mortality). Some patients' weights were recorded based on the parental estimation or using the Broselow tape in case of emergencies. The underlying medical conditions were defined as any co-morbidities that might affect the patient's current health status, including a wide array of respiratory, cardiovascular, neurologic, malignancy, metabolic, genetic, and immune deficiency disorders, among others. The reasons for conducting ETI interventions on our current study patients included respiratory compromise, an altered mental status, shock, and others. RSI medication use did not include any sedatives or NMBAs use for any purpose other than ETI. Physiologic adverse events were positive if any desaturation, hypotension or bradycardia newly occurred during or soon after the ETI. Desaturation was defined as a peripheral oxygen saturation below 90%, a fall of more than 10% or worsening cyanosis. Hypotension and bradycardia were determined using an age-based normal range defined by the Pediatric Advanced Life Support guidelines.[13] Several clinicians in each institution collected the data, and co-authors made their final agreements after a detailed review.

Data analysis

The data characteristics of the patients and ETI were reported as numbers (percentage), except for the non-normally distributed continuous variables (patient age, weight, door-to-successful ETI time, and ventilator days) as median (IQR). The study cases were classified into three groups in accordance with the use of RSI medication (i.e., no-medication, sedative-only, and sedative-with-NMBA groups). The characteristics of these groups were compared using a Pearson's chi-square or Krus-

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kal-Wallis test (followed by a Mann-Whitney U test) with Bonferroni correction. Multivariable logistic regression analyses (enter method) were conducted using selected variables with p values <0.1 determined by univariable analysis after exploring their collinearity. Trends for RSI medication use stratified by the patient group and according to a 2-year-interval in patient age were tested using linear-by-linear associations. All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). p values <0.05 were considered statistically significant.

Ethics statement

Institutional review board approval was obtained at the lead site (Ajou University Hospital; AJIRB-MED-MDB-21-419) and at all other participating sites. The requirement for informed consent from patients was waived due to the retrospective study design.

RESULTS

Characteristics of study population and ETI procedures

Of the 537 eligible pediatric emergency ETI that were initially identified by the database searches, 334 cases were finally included after excluding 203 cases (Fig. 1). The included cases stratified by participating hospitals are listed in Supplementary Table 1 (only online). Among the study population, six patients had multiple ETI on separate ED visits (one patient with four procedures, two patients with three procedures, and three patients with two procedures), and these repeat interventions were treated as additional cases. The characteristics of the study patients, intubators, RSI medications, and outcomes are shown in Table 1. The median age of the children was 3.4 years (IQR, 0.8–10.7), and 28.4% were infants. Underlying medical conditions were noted in 57.5% of the population, including six cases of neuromuscular disorders. Respiratory compromise (49.4%) was the most common reason for conducting an ETI. The ETI procedures were usually performed in the ED (73.1%) by pediatricians (50.3%) and residents (60.8%), rather than by attending physicians. Sedatives and NMBAs were used in 63.8% and 32.9% of the study cases, respectively, with midazolam (48.4%) and succinylcholine (51.8%) being the mostly commonly used agents. The first-attempt success rate was 66.2%, and the overall success rate was 100%. Physiologic adverse events were noted in 30.5% of the cases, with desaturation being most common.

Group comparisons in accordance with RSI medication use

A total of 334 cases were classified into the no-medication (n=121), sedative-only (n=103), and sedative-with-NMBA (n=110) groups (Fig. 1), and their characteristics were then compared (Table 2). The patient age, underlying medical conditions, and pediatricians as intubators were found to be significantly different variables among the groups. The no-medication group showed the youngest median age (1.0 year), a larger proportion of underlying medical conditions (77.7%), and pediatricians as intubators (76.9%). In contrast, the sedative-with-NMBA group showed the highest median age (11.3 years) and the smallest proportion of both underlying medical conditions (36.4%) and pediatricians as intubators (17.3%). With regard to the types of sedatives incorporated in the ETI protocols, etomidate (51.8%) was most commonly used in the sedative-with-NMBA group cases, whereas midazolam (61.2%) and ketamine (20.4%), rather than etomidate, were more frequently employed in the sedative-only group. Although the overall physiologic adverse events were lower in the sedative-with-NMBA group than in the no-medication or sedative-only groups, the difference was not statistically significant (p=0.297).

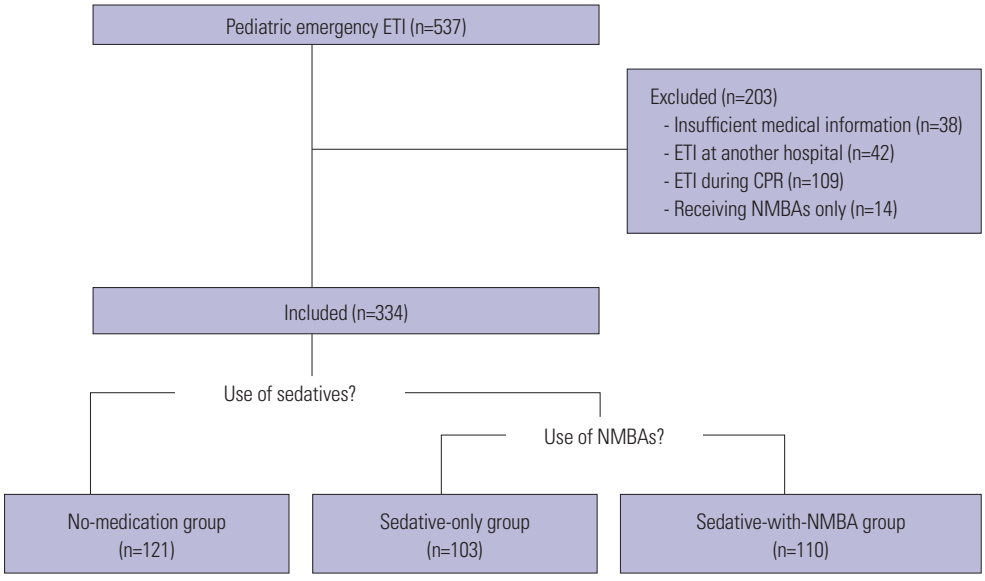

Fig. 1. Flowchart of study population. CPR, cardiopulmonary resuscitation; ETI, endotracheal intubation; NMBA, neuromuscular blocking agent.

Table 1. Characteristics of Study Population and ETI Procedures (n=334)

Characteristics	Values
Age, yr	3.4 (0.8–10.7)
Infant (<1)	95 (28.4)
Child (1–9)	152 (45.5)
Adolescent (10–17)	87 (26.0)
Sex, male	197 (59.0)
Weight, kg	11.9 (5.7–29.3)
Underlying medical conditions (n=192)	192 (57.5)
Neurologic	56 (29.2)
Cardiovascular	34 (17.7)
Respiratory	29 (15.1)
Others	73 (38.0)
Reason for ETI	
Respiratory compromise	165 (49.4)
Altered mental status	119 (35.6)
Shock	46 (13.8)
Others	4 (1.2)
Door-to-successful ETI time, min	58 (21–231)
ETI-performed place	
EDs	244 (73.1)
Intensive care units	86 (25.7)
Wards	1 (0.3)
Others	3 (0.9)
Intubator's specialty	
Pediatrics	168 (50.3)
Emergency medicine	108 (32.3)
Surgery	52 (15.6)
Others*	6 (1.8)
Intubator's professional status	
Resident	203 (60.8)
Attending	131 (39.2)
Sedatives (n=213)	213 (63.8)
Midazolam	103 (48.4)
Etomidate	73 (34.3)
Ketamine	30 (14.1)
Others†	7 (3.3)
NMBA (n=110)	110 (32.9)
Succinylcholine	57 (51.8)
Vecuronium	48 (43.6)
Rocuronium	5 (4.5)
No. of attempts for successful ETI	
1	221 (66.2)
2	66 (19.8)
≥3	47 (14.1)
Physiologic adverse events	102 (30.5)
Desaturation	81 (24.3)
Hypotension	32 (9.6)
Bradycardia	18 (5.4)
Ventilator days	4 (2–10)
In-hospital mortality	43 (12.9)

ED, emergency department; ETI, endotracheal intubation; NMBA, neuromuscular blocking agent.
The values are expressed as the median (IQR) or number (%).
*Anesthesiology and internal medicine; †Sedatives included propofol and lorazepam.

Factors associated with RSI medication use

Multivariable logistic regressions were conducted for the sedative-only and sedative-with-NMBA cases. The factors associated with sedative use included patient age [for a year increment; adjusted odds ratio (aOR), 1.183; 95% confidence interval (CI), 1.108–1.263], no underlying medical conditions (aOR, 3.760; 95% CI, 2.016–7.013), intubators other than pediatricians (aOR, 3.187; 95% CI, 1.591–6.384), and ETI due to respiratory compromise (aOR, 2.349; 95% CI, 1.285–4.294) (Table 3). The factors associated with sedatives with NMBA use were patient age (for a year increment; aOR, 1.182; 95% CI, 1.120–1.249), no underlying medical conditions (aOR, 2.109; 95% CI, 1.093–4.070), and intubators other than pediatricians (aOR, 5.123; 95% CI, 2.257–11.626) (Table 4). The trends in relation to sedatives and NMBA use demonstrated age-related increases (p for trend< 0.001) (Fig. 2).

DISCUSSION

Our current multicenter study of 334 pediatric emergency ETI demonstrates an ongoing underuse of RSI medications in Korea, which was found to be associated with a younger patient age, underlying medical conditions, and pediatricians as intubators. These findings contribute to our understanding of pediatric emergency ETI in Korea, and provide considerations that may help to promote the clinical use of RSI.

Patient age is a significant factor in relation to RSI medication use in a pediatric emergency ETI, which may have contributed to the observed underuse of NMBAs in the present study. Although the proportion of NMBA use (30.6%) among the current study population was found to be increased from the 12% reported by a previous Korean registry-based study, it was still much lower than the 81% level described in the NEAR registry-based study from the U.S.[5,12] The median patient age of 3.4 years in the present study cohort was lower than that of the NEAR registry-based study population (7 years).[5] The NEAR study demonstrated a lower frequency of NMBA use in children aged under 2 years than in older cases (61% vs. 87%).[5] The results from our current comparisons among the case groups according to RSI medication use also demonstrated significant differences in patient age (i.e., a higher patient age of 11.3 years in the sedative-with-NMBA group compared to 1.0 years in the no-medication group and 2.8 years in the sedative-only group). Furthermore, our multivariable regressions verified that an increasing patient age was a significant factor for both NMBA and sedative use. The significance of the children's age in this clinical context is also supported by our finding of age-related increases in RSI medication use in the trend analyses.

Based on these aforementioned results, we speculate that a younger patient age may be an obstacle to the widespread use of RSI. In this regard, we also suppose that the reluctance to administer RSI medications for pediatric ETI is influenced by

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Table 2. Comparative Analysis of No-Medication, Sedative-Only, and Sedative-with-NMBA Groups

Variable	No-medication group (n=121)	Sedative-only group (n=103)	Sedative-with-NMBA group (n=110)	*p* value
Age, yr	1.0 (0.3–3.3)	2.8 (0.8–7.2)	11.3 (4.6–16.2)	<0.001*
Age group, yr				
Infant (<1)	58 (47.9)	27 (26.2)	10 (9.1)	<0.001*
Child (1–9)	54 (44.6)	59 (57.3)†	39 (35.5)†	0.006
Adolescent (10–17)	9 (7.4)†	17 (16.5)‡	61 (55.5)†‡	<0.001
Underlying medical conditions	94 (77.7)	58 (56.3)	40 (36.4)	<0.001*
Neurologic	27 (22.3)	15 (14.6)	14 (12.7)	0.116
Cardiovascular	17 (14.0)†	12 (11.7)	5 (4.5)†	0.049
Respiratory	15 (12.4)	8 (7.8)	6 (5.5)	0.160
Pediatricians as intubators	93 (76.9)	56 (54.4)	19 (17.3)	<0.001*
Attending physicians as intubators	29 (24.0)†‡	41 (39.8)†	61 (55.5)‡	<0.001
Type of sedatives				
Midazolam	-	63 (61.2)	40 (36.4)	<0.001
Etomidate	-	16 (15.5)	57 (51.8)	<0.001
Ketamine	-	21 (20.4)	9 (8.2)	0.010
No. of attempts for successful ETI	1 (1–2)	1 (1–2)	1 (1–2)	0.150
First-attempt success	79 (65.3)	62 (60.2)	80 (72.7)	0.150
Physiologic adverse events	43 (35.5)	30 (29.1)	29 (26.4)	0.297
Desaturation	36 (29.8)	23 (22.3)	22 (20.0)	0.194
Hypotension	12 (9.9)	8 (7.8)	12 (10.9)	0.729
Bradycardia	7 (5.8)	5 (4.9)	6 (5.5)	0.953
Ventilator days	6 (2–14)	4 (1–7)	4 (2–10)	0.161
In-hospital mortality	21 (17.4)	10 (9.7)	12 (10.9)	0.177

ETI, endotracheal intubation; NMBA, neuromuscular blocking agent.
The values are expressed as the median (IQR) or number (%). Pearson's chi-square or Kruskal-Wallis tests (followed by a Mann-Whitney U test) with Bonferroni correction were conducted.
*Significant differences were noted between all groups; †‡Significant differences were noted between the groups.

Table 3. Factors Associated with Sedative Use in Pediatric ETI

Variables	aOR (95% CI)	*p* value
No underlying medical conditions	3.760 (2.016–7.013)	<0.001
Intubators other than pediatricians	3.187 (1.591–6.384)	0.001
ETI due to respiratory compromise	2.349 (1.285–4.294)	0.006
Age (for a year increment)	1.183 (1.108–1.263)	<0.001
Attending physicians as intubators	1.725 (0.894–3.330)	0.104
ETI performed at the emergency department	0.717 (0.379–1.359)	0.307

ETI, endotracheal intubation; aOR, adjusted odds ratio; CI, confidence interval.
Multivariable logistic regression using the enter method was conducted.

Table 4. Factors Associated with the Combined Use of Sedatives and NMBAs

Variables	aOR (95% CI)	*p* value
Intubators other than pediatricians	5.123 (2.257–11.626)	<0.001
No underlying medical conditions	2.109 (1.093–4.070)	0.026
Age (for a year increment)	1.182 (1.120–1.249)	<0.001
Attending physicians as intubators	1.686 (0.863–3.292)	0.126
ETI due to respiratory compromise	1.388 (0.700–2.750)	0.347
ETI performed at the emergency department	0.468 (0.196–1.122)	0.089

ETI, endotracheal intubation; NMBA, neuromuscular blocking agent; aOR, adjusted odds ratio; CI, confidence interval.
Multivariable logistic regression using the enter method was conducted.

an excessive anxiety over possible adverse events in a young child, as well as uncertainty about the harm that could result from sedatives and NMBAs in these cases. Indeed, it is known that younger children are more prone to desaturation from relatively high oxygen consumption and can have low functional residual capacity and bradycardia from a prominent vagal reflex.[14-16] However, it is unlikely that sedatives or NMBAs will increase the risk of adverse events during ETI procedures in children, as they are more likely to occur due to the ETI procedure itself (such as prolonged intubation attempts) and other related causes.[17,18] RSI itself shortens the time required to conduct the ETI, eases the procedure, and ultimately lowers the incidence of adverse events.[3] When using broader definitions of complications from an ETI, such as vomiting or other technical problems, previous studies have reported that RSI was associated with a significantly reduced rate of such adverse events.[4,6] Although we could not investigate the overall incidence and types of adverse events in our present study cases due to its retrospective design, the frequency of physiologic events, particularly desaturation, seemed lower in the sedative-with-NMBA group than in the other groups.

We defined underlying medical conditions as any co-morbidities that might affect the patient's current health status, in-

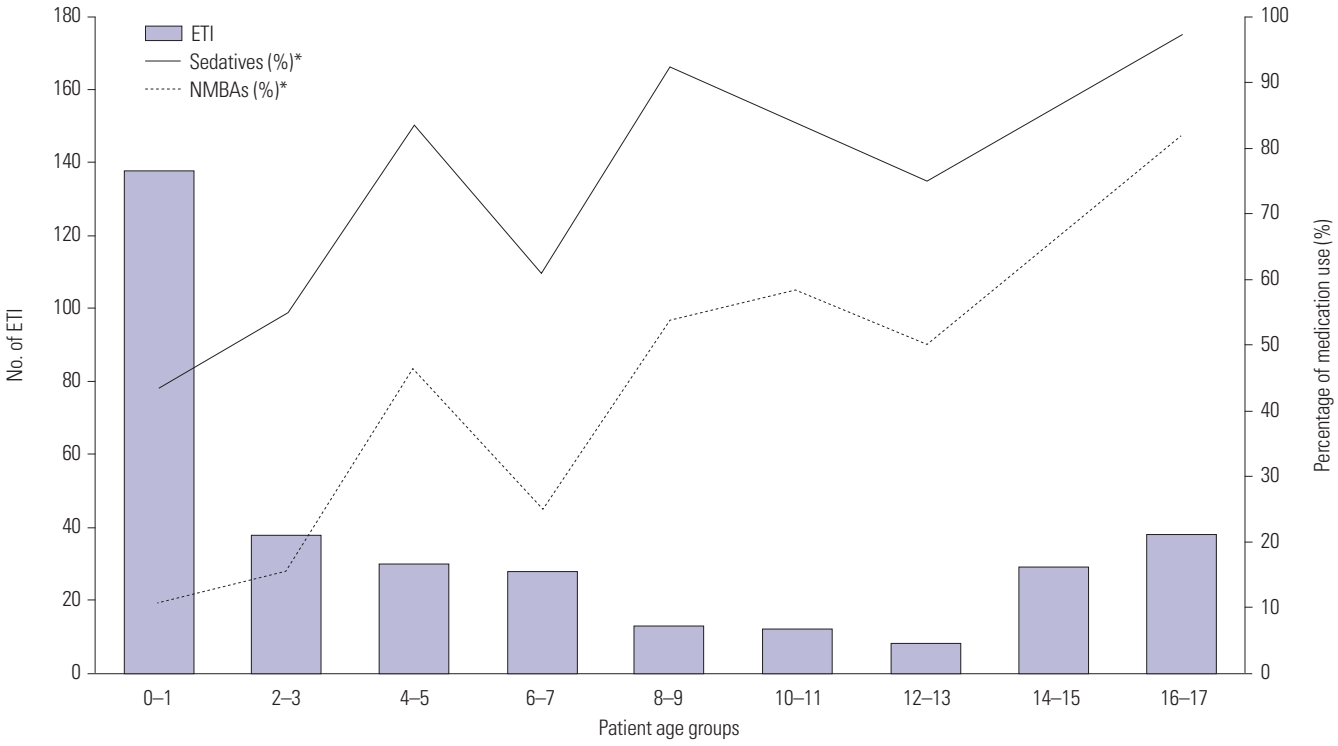

Fig. 2. Trends for sedative and NMBA use during ETI in accordance with the age of children. *Tests for these trends were conducted using linear-by-linear association (*p* for trend<0.001). ETI, endotracheal intubation; NMBA, neuromuscular blocking agent.

cluding epilepsy or diabetes mellitus, and thus not limited to neuromuscular or airway affecting disorders. Nevertheless, the absence of underlying medical conditions among our present study population was significantly associated with RSI medication use. We again speculate that this was due to a somewhat overly cautious reluctance to the use of sedatives and NMBAs in children with any underlying medical conditions. Pediatricians accounted for 50.3% of the clinicians who conducted the intubation procedures, and this variable was found to be significantly associated with the underuse of RSI medications. This tendency of pediatricians is possibly related to an insufficient translation of the adult-driven RSI methods into pediatric emergency medical practice in Korea.[19] Furthermore, the frequent use of midazolam (48.4%) may be attributable to the familiarity of pediatricians with its antiepileptic indication.[20] However, midazolam has disadvantages, such as a slower onset, and thus seems inappropriate for the RSI method.[3,21] We suggest developing a set of dedicated guidelines for RSI in a pediatric emergency ETI setting and implementing training for pediatricians to ease their reluctance to use RSI medications in children, particularly those who are very young or have underlying medical conditions.[22,23]

The results of the present study confirmed that respiratory compromise (49.4%) is the most common reason for an ETI intervention in children, and that it was associated with sedative use (p=0.006) but not with the administration of NMBAs (p=0.347). Respiratory compromise seems to confer a greater need for sedative use with ETI in children than other conditions, such as shock, because they usually do not affect the mental status of children who also have the tendency to develop hypoxia-induced agitation. The first-attempt success rate with ETI (66.2%) in our current study cohort is similar to that described by the prior Korean registry-based study (68%), but lower than the rate in the NEAR registry-based report (83%).[5,12] Similar to previous studies,[4,5] the first-attempt success rate in this present study was higher in the sedative-with-NMBA group (72.7%) than in the sedative-only (60.2%) or the no-medication (65.3%) group, although without statistical significance. Although other explanations are possible, we suggest from this finding that the higher proportion of attending physicians conducting the ETI (39.2%) in this study than in the NEAR registry-based study (83% of the procedures were done by trainees) may have reduced the differences in the first-attempt success rates between the groups due to their greater clinical experience.[5,24]

This study had several limitations. First, our data were collected from four academic hospitals in Korea, and the results might not be readily applicable to other emergency settings or other countries. Second, the collected data may have had some errors due to the retrospective study design. For instance, the first-attempt success rate is known to be overestimated despite the underreporting of intubation failures.[5,25] To overcome such errors, we additionally reviewed nursing records on the ETI process rather than exclusively depending on physician procedure notes, which supported the general reliability of the data. Third, we did not evaluate the inter-rater reliability of the collected data. Additionally, we did not analyze the use of atropine, dif-

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ficult airway situations, apneic oxygenation, video laryngoscopy or external laryngeal manipulation, all of which could affect the clinical outcomes.[26]

In conclusion, the proportion of RSI procedures that use sedatives and NMBAs in a pediatric emergency ETI setting was only 32.9% in Korea. This underuse of RSI medications is associated with younger patient age, underlying medical conditions, and pediatricians as intubators.

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AUTHOR CONTRIBUTIONS

Conceptualization: Jeong-Yong Lee and Jung Heon Kim. Data curation: all authors. Formal analysis: Jeong-Yong Lee and Jung Heon Kim. Funding acquisition: Jeong-Yong Lee. Investigation: all authors. Methodology: Se Uk Lee, Meong Hi Son, Joong Wan Park, and Jae Yun Jung. Project administration: Jae Yun Jung. Resources: all authors. Software: Jeong-Yong Lee. Supervision: Jae Yun Jung. Validation: Jeong-Yong Lee and Jung Heon Kim. Visualization: Jeong-Yong Lee. Writing—original draft: Jeong-Yong Lee. Writing—review & editing: Se Uk Lee, Meong Hi Son, Joong Wan Park, Jae Yun Jung, and Jung Heon Kim. Approval of final manuscript: all authors.

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