Considerations for physicians using ketamine for sedation of children in emergency departments

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Objective Ketamine use in emergency departments (EDs) for procedural sedation and analgesia is becoming increasingly common. However, few studies have examined patient factors related to adverse events associated with ketamine. This study investigated factors for consideration when using ketamine to sedate pediatric ED patients.

Methods The study included pediatric patients receiving ketamine for laceration repair in the ED. Before sedation, information was collected about upper respiratory tract infection symptoms, allergy history, and fasting time. Patients received 2 mg/kg ketamine intravenously or 4 mg/kg ketamine intramuscularly. The primary outcomes were adverse events due to ketamine.

Results We studied 116 patients aged 8 months to 7 years (2.8±1.5 years). The group with adverse events was significantly younger on average than the group without adverse events (2.5±1.5 vs. 3.1±1.5, P=0.028). Upper respiratory tract infection symptoms were not significant variables affecting ketamine sedation (48.9% vs. 43.7%, P=0.719). There was no significant association between duration of fasting and adverse events (P=0.073 and P=0.897, respectively), or between food type and adverse events (P=0.734). However, the number of attempts to sedate and ketamine dose correlated with adverse events (P<0.001 and P=0.022, respectively). In multiple logistic regression analysis, intravenous injection and ketamine dose were significant factors (odds ratio, 16.77; 95% confidence interval, 1.78 to 498.54; odds ratio, 4.37; 95% confidence interval, 1.59 to 22.9, respectively).

Conclusion Emergency medicine physicians should consider injection type and ketamine dose when using ketamine sedation while suturing lacerations.

Keywords Emergency service, hospital; Ketamine; Pediatric sedation; Adverse events; Monitoring

Capsule Summary

What is already known
Ketamine is commonly used in the emergency department for pediatric sedation. However, patient factors associated with adverse events are poorly described.

What is new in the current study
Injection type and dose are associated with adverse events in children sedated with ketamine in the emergency department.

INTRODUCTION

Patients in the emergency department (ED) often face extreme pain and anxiety from emergency procedures. To reduce their pain and anxiety, procedural sedation and analgesia are administered. Unlike general anesthesia, procedural sedation and analgesia achieve analgesia with sedation, such that patients can control their breathing on their own. In particular, pediatric trauma patients usually require sedatives. Although sedatives used in these cases are safe and have a short half-life, sedative use requires close monitoring because of potential serious adverse consequences that depend on the patient. However, monitoring itself is sometimes challenging in a busy ED.

Ketamine, a derivative of phencyclidine, is the most commonly used sedative and an ideal pediatric sedative in the ED.[1,2] Oral sedatives, such as chloral hydrate, are also used,[3] but they have unfavorable side effects, such as nausea, vomiting, agitation, restlessness, a longer recovery time, and high failure rates of up to 20%.[4] Ketamine inhibits the cerebral cortex and stimulates the limbic system, causing dissociation of the central nervous system from strong external stimuli.[1,5,6] As a result, strong analgesia, sedation, or memory loss can be achieved using ketamine. However, ketamine also causes hypoxia, laryngospasm, apnea, bradycardia, hypersalivation, vomiting, and recovery agitation.[7]

One of the most worrying adverse events associated with sedatives is tracheal aspiration of regurgitated food; therefore, guidelines suggest that sedatives or analgesics should be administered on an empty stomach.[8] However, although many institutions follow this guideline, several recent studies have reported that no association exists between preprocedural fasting state and adverse events from sedation.[9,10] In addition, the clinical policy of the American College of Emergency Physicians published in 2014 recommended proceeding with sedation in the ED regardless of the fasting state, since preprocedural fasting does not reduce the risk of vomiting or aspiration.[11] However, the American Academy of Pediatrics and American Society of Anesthesiologists guidelines suggest that the requirement for fasting before sedation depends on the type of food consumed and whether it is solid or liquid.[8,12] However, the American Academy of Pediatrics guidelines also mentioned that the use of agents with less risk of depressing protective airway reflexes, such as ketamine, may be preferred for emergency patients.[12]

The purpose of this study was to analyze factors affecting adverse events related to ketamine administration in the pediatric population in the ED using a checklist and the establishment of key elements to consider in sedation using ketamine.

METHODS

Study design and population

This prospective observational study examined pediatric patients with simple lacerations requiring suturing from January to April 2016. Pediatric patients who would not co-operate with local anesthesia and who required sedation were included. All included patients were sedated using only ketamine. Patients were excluded for the following reasons: if they were younger than 3 months; had factors that elevated intraocular pressure (such as known glaucoma or acute globe injury) or intracranial pressure (such as known central nervous system masses, abnormalities, or hydrocephalus); had head trauma associated with loss of consciousness; had a previous allergic reaction to ketamine; or had parents who declined to participate in the study.

Study protocol

A standardized worksheet was created, and patient details pre- and post-ketamine administration were recorded. These included fasting duration, presence of upper respiratory tract infection symptoms (cough, runny nose, and sputum), allergic reaction, sedation time and frequency, vital signs, route of ketamine administration, adverse events, and procedures when adverse events occurred. The patients were divided into group with adverse events (GWAE) and group without adverse events (GWOAE). Patients with at least one adverse event were allocated to GWAE, and the remaining patients were allocated to GWOAE. To identify key elements related to adverse events, the factors of each group recorded in a checklist were compared. Adverse events included recovery agitation, involuntary movement, hypersalivation, vomiting, hypoxia, laryngospasm, cyanosis, apnea, and bradycardia. Hypoxia was defined as oxygen saturation <95%, and laryngospasm was characterized by stridor or retraction. Apnea was defined as the cessation of respiratory airflow. The length of time of cessation was 20 seconds or shorter if associated with bradycardia or cyanosis. Bradycardia was defined as a pulse below 60 beats/min (for a child older than two years) or a pulse below 80 beats/min (for a child younger than two years).

Subjects were closely monitored by one emergency medicine resident and one paramedic from the time of ketamine administration to complete recovery of consciousness, and an emergent airway management kit was made readily available next to the subjects. Resuscitative efforts included repositioning of the airway, oxygen administration and oropharyngeal airway insertion or intubation. All subjects were sedated with ketamine without local anesthesia for suturing, which was performed by a plastic surgeon.

All patients received 2 mg/kg ketamine intravenously (IV) or 4 mg/kg ketamine intramuscularly (IM), according to the clinical situation.

In the IV group, the initial dose was 2 mg/kg over 1 to 2 minutes under the supervision of an emergency medicine physician. If necessary, an additional 1 mg/kg was administered. In the IM group, the initial dose was 4 mg/kg, followed by an additional 2 mg/kg if necessary.

Sedation induction time was defined as the time taken from administration to achieve appropriate sedation. The discharge criteria were as follows: appropriate oxygenation, alert to voice or light touch, stable airway during swallowing, and recovery of consciousness. The criteria for recovery of consciousness included age-appropriate language, recognition of parents/guardians, and purposeful movement, based on the Vancouver sedation scale.[13]

This study was approved by the institutional review board of Soonchunhyang University Hospital (2016-05-003-002), and the authors agreed on the study objective and protocol, and about procedural sedation and analgesia. The emergency medicine physician obtained consent from the parents/guardians of each patient.

Analysis and statistics

General characteristics of the study groups divided according to adverse events were summarized as mean±standard deviation for quantitative variables, and frequency (percentage) for qualitative variables. To compare the quantitative characteristics between the two groups, a Student's t-test or Mann-Whitney U-test was used as appropriate, according to the result of a normality and equivalent-variance test with Shapiro-Wilk test and Levene's test. A chi-square test was used to compare the qualitative variables.

Univariate logistic regression analysis was performed to examine the effect of candidate parameters on the occurrence of adverse events. For each parameter, the odds ratio (OR) for the risk of the adverse event was expressed with a 95% confidence interval (CI). For the multivariable logistic regression analysis, the Akaike information criterion-based backward selection method was used to exclude insignificant variables from the initial regression model, including factors considered statistically and clinically significant. Multiple collinearity of the continuous variables was assessed using generalized variance inflation factors.

A two-tailed P-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS ver. 14.0 (SPSS Inc., Chicago, IL, USA) and R ver. 3.1.3 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

There were 116 subjects: 45 in the GWAE and 71 in the GWOAE. There were 87 in the IV group and 29 in the IM group. The mean patient age was 2.8±1.5 years (range, 8 months to 7 years). The propor-

tion of male subjects was 67.2%. The mean procedure time (from appropriate sedation to completion of procedure) was 11.5±8.6 minutes. The mean fasting duration was 3.8±1.7 hours.

Age and number of trials to sedation differed statistically between GWAE and GWOAE (2.5±1.5 vs. 3.1±1.5 years, P=0.028; 1.3±0.6 vs. 1.0±0.1, P<0.001, respectively). The ketamine dose (mg/kg) also differed significantly between the two groups (GWAE 2.9±1.1 vs. GWOAE 2.5±0.9, P=0.022) (Table 1).

Although there was no statistical difference, the procedure time was slightly longer in GWAE (14.3±12.4 vs. 9.8±4.3 minutes, P=0.341) (Table 1).

Adverse events according to presedation factors
Univariate logistic regression analysis
Three presedation factors were statistically related to adverse events: procedure time (minutes; OR, 1.07; 95% CI, 1.02 to 1.14; P=0.015); number of attempts required to sedate (OR, 13.38;

Table 1. Baseline characteristics according to adverse events

Variable	GWAE (n=45)	GWOAE (n=71)	P-value
Demographic factor			
Age (yr)	2.5±1.5	3.1±1.5	0.028
Sex			0.922
Male	31 (68.9)	47 (66.2)	
Female	14 (31.1)	24 (33.8)	
BMI (kg/m²)	16.6±3.9	15.9±2.4	0.359
ED arrival data			
Body temperature (°C)	36.6±0.3	36.6±0.4	0.820
URI symptoms	22 (48.9)	31 (43.7)	0.719
Type of food			0.734
Solid	25 (55.6)	43 (60.6)	
Liquid	20 (44.4)	28 (39.4)	
Fasting duration (hr)	3.5±1.7	4.0±1.7	0.073
Fasting duration (hr)[a]			0.897
Within criteria	14 (31.1)	20 (28.2)	
Beyond criteria	31 (68.9)	51 (71.8)	
Treatment to sedation			
Procedure time (min)	14.2±12.3	9.8±4.4	0.341
No. of attempts to sedate (n)	1.3±0.6	1.0±0.1	<0.001
Injection type of ketamine			0.582
IV	32 (71.1)	55 (77.5)	
IM	13 (28.9)	16 (22.5)	
Dose of ketamine (mg/kg)	2.9±1.1	2.5±0.9	0.022

Data are presented as mean±standard deviation for continuous variables and frequency (%) for categorical variables. P-values were calculated using a Student's t-test or Mann-Whitney U-test for continuous variables and chi-square test for categorical variables.
GWAE, group with adverse events; GWOAE, group without adverse events; BMI, body mass index; ED, emergency department; URI, upper respiratory infection; IV, intravenous; IM, intramuscular.
[a]Within criteria: fasting duration ≥2 hours for liquid food and ≥6 hours for solid food.

Table 2. Logistic regression analysis for adverse events

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P–value	OR (95% CI)	P–value
Age (yr)	0.77 (0.58–1.00)	0.060		
Female	0.88 (0.39–1.96)	0.763		
BMI (kg/m^2)	1.08 (0.95–1.24)	0.241		
Body temperature (°C)	0.74 (0.23–2.23)	0.594		
URI symptoms	1.23 (0.58–2.62)	0.582		
Solid food	0.81 (0.38–1.74)	0.594		
Fasting duration (hr)	0.83 (0.66–1.04)	0.105	0.83 (0.64–1.05)	0.130
Fasting duration beyond criteria (hr)	0.87 (0.39–1.99)	0.735		
Procedure time (min)	1.07 (1.02–1.14)	0.015		
No. of attempts to sedate (n)	13.38 (2.83–243.79)	0.012		
IV injection	0.72 (0.31–1.70)	0.442	16.77 (1.78–498)	0.034
Dose of ketamine (mg/kg)	1.48 (1.02–2.19)	0.043	4.37 (1.59–22.9)	0.018

OR, odds ratio; CI, confidence interval; BMI, body mass index; URI, upper respiratory infection; IV, intravenous.
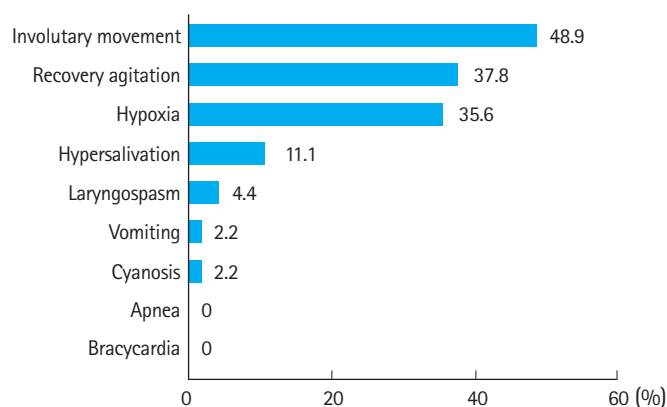
Fig. 1. Proportion of adverse events.

95% CI, 2.83 to 243.79; P = 0.012); and dose of ketamine (mg/kg; OR, 1.48; 95% CI, 1.02 to 2.19; P = 0.043). However, there were no significant associations between adverse events and age, URI symptoms, or fasting duration (P = 0.06, P = 0.582, and P = 0.735, respectively) (Table 2).

Multivariate logistic regression analysis
Adverse events were significantly related to IV injection (OR, 16.77; 95% CI, 1.78 to 498.54; P = 0.034) and ketamine dose (OR, 4.37; 95% CI, 1.59 to 22.9; P = 0.018) (Table 2). In the multivariate logistic regression analysis, procedure time, number of attempts required to sedate, and fasting duration were not significantly related to adverse events.

Proportion of adverse events
The most frequent adverse event was involuntary movement (48.9%). Other adverse events included recovery agitation (37.8%), hypoxia (13.8%), and hypersalivation (11.1%) (Fig. 1).

DISCUSSION

Ketamine, which can be administered both IV and IM, is one of the most commonly used sedatives in pediatric cases.[6] There are several key elements to consider when using ketamine for sedation in children; these are patient age, upper respiratory infection symptoms, injection route, and fasting period. Physicians using ketamine should consider the patient's condition and all factors related to the adverse events of ketamine. The most frequent adverse events observed in this study were involuntary movement and recovery agitation, and this is consistent with the results of other studies.[14,15]

This study enrolled pediatric patients. Therefore, we used the normal vital sign values in children that have been described in many previous studies. We defined hypoxia as an oxygen saturation < 95%[16] and bradycardia as a pulse rate < 60 beats/min (for a child older than two years) or < 80 beats/min (for a child younger than two years).[17] Apnea was defined as the cessation of respiratory airflow for 20 seconds or less if associated with bradycardia or cyanosis.[18]

Previously published guidelines state that use of ketamine is relatively contraindicated in patients with lung diseases, such as asthma or upper respiratory infections.[6] The current study, however, found no significant relationship between adverse events and upper respiratory tract infection symptoms (P = 0.582). If clinicians were to monitor O$_2$ saturation in patients with upper respiratory tract infection symptoms more closely after administration of ketamine, the presence of such symptoms would not be a major concern with ketamine use.

This study found a statistically significant relationship between younger age and the likelihood of having an adverse event. How-

ever, a recent study showed an increased rate of vomiting after ketamine use as patient age increased (7 vs. > 12 years; 20.6% vs. 50%).[19] In addition, other studies have shown a positive correlation between age and rate of adverse events from ketamine (8.2 vs. 5.2 years, P = 0.001).[9] In the current study, the age difference between the GWAE and the GWOAE was 0.6 years (7.2 months). This difference is statistically significant; however, the difference is small in clinical terms. A future study involving a larger patient sample with a broader age range would be beneficial for identifying a relationship between age and adverse events from ketamine.

This study also found no significant relationship between fasting duration and adverse events. We analyzed fasting duration beyond reported criteria.[8,12] Another recent study found that fasting duration was significantly related to adverse events, especially vomiting, although hypoxia was not.[10] A future study investigating the depth of sedation in more subjects would be valuable for understanding the relationship between fasting duration and adverse events.

Another study found that the likelihood of vomiting increased from 3.8% to 29% as fasting duration decreased.[20] In addition, it was reported that vomiting occurred after the procedure in up to 14% of cases, although no cases experienced vomiting in the middle of the procedure.[19] In this study, there was only one case of vomiting (< 1%) during the procedure. A future study on the rate of ketamine-induced vomiting after discharge would add useful insight in clinical practice. However, based on recent evidence,[9,19] physicians should perform the procedure regardless of the fasting period to provide shorter ED stays, effective flow management, and the prevention of overcrowding in the ED.

In this study, there was a significant difference in the rate of adverse events according to the route of administration. In the multivariate logistic regression analysis, the OR of IV ketamine was 16.77 (95% CI, 1.78 to 498.54; P = 0.034). IV administration was also significantly related to adverse events of ketamine in other studies.[4,15,21] In our series, the IV group was larger than the IM group (87 vs. 29 patients) and the 95% CI was too wide. In a future study, IM and IV groups with similar numbers may be required to obtain reliable results. Previous studies have demonstrated a sedation induction time of 30 to 60 seconds via the IV route and 3 to 5 minutes via the IM route.[22,23] The current study found mean sedation induction times of 54 seconds (IV) and 4.6 minutes (IM), which are consistent with those described in the recent literature.

The subjects in this study were discharged to home without any serious adverse events. The minor adverse events in the current study were temporary and managed appropriately. One pre-

vious study concluded that ketamine is a relatively safe sedative regardless of atropine use.[24] A second study also reported no serious complications from sedative use in pediatric patients in the ED, with an adverse event rate of 2.3%.[25] In another study, no serious complications associated with ketamine administration at doses 5 to 100-fold higher than recommended (administered in error) were reported, except for minor temporary respiratory distress or prolonged sedation.[26] Although this study found two cases of laryngospasm, they were mild in nature. According to current evidence, the rate of serious complications, such as laryngospasm or apnea, is 0.4% to 1.4%.[21,27] In summary, ketamine is a safe sedative to use in pediatrics, with readily available resources for possible airway management.

This study focused on ketamine use only in the suturing of lacerations without local anesthesia. A comparison of ketamine versus local anesthesia during laceration suturing would advance our understanding of the choice of pain control. In addition, a further study on the effects of ketamine in different procedures related to dislocation, fractures, endoscopy, or foreign body removal would help clinical practices in minimizing adverse events.

The limitations of this study were the small sample size, the short duration of the study period, and the fact that researchers did not investigate all pediatric patients who presented to the ED with lacerations. Therefore, there was a possibility of selection bias.

This study was conducted until the end of the suturing procedure. The patients were monitored until discharge. There was no record of adverse events during the recovery period after sedation and discharge from the ED. More research is needed in a future study to address these limitations.

In summary, when administering ketamine sedation in ED pediatric patients undergoing suturing for lacerations, clinicians should consider the possibility of adverse events, which can be influenced by injection type and ketamine dose.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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