Emergency Department Ketamine Sedation: Frequency and Predictors of Critical and High-Risk Adverse Events

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Study objectives: We wished to assess the frequency of critical and high-risk adverse events when ketamine is administered for emergency department (ED) procedural sedation in children and to identify clinical predictors of such adverse events.

Methods: We studied 20 years of sedation encounters from the Pediatric Sedation Research Consortium registry. We descriptively report the frequencies of critical and high-risk adverse events and evaluate their associations with clinical variables.

Results: Of the 12,780 unique ED ketamine encounters, there were 2 children with critical adverse events (0.016%; 95% confidence interval [CI] 0.0019 to 0.057): 1 occurrence of suspicion for pulmonary aspiration without desaturation, intubation, or unplanned hospitalization, and 1 occurrence of anaphylaxis with unplanned hospitalization. There were 67 children with high-risk events (0.52%; 95% CI 0.41 to 0.66), including 41 occurrences of positive pressure ventilation, 36 of apnea, and 7 of laryngospasm. Predictors of either critical or high-risk adverse events were age more than or equal to 10 years and administered opioids. Higher American Society of Anesthesiologists physical status, upper respiratory infection, and obstructive sleep apnea were not predictive.

Conclusion: In this largest yet study of ketamine as a sole agent for ED pediatric procedural sedation, we found that critical adverse events were rare and high-risk events uncommon. Modest predictors of these events were age more than or equal to 10 years and administered opioids. [Ann Emerg Med. 2025;■:1-6.]

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INTRODUCTION

Background

For more than 3 decades, ketamine has been the most popular parenteral sedative to facilitate painful or anxiety-inducing emergency department (ED) procedures in children.[1-5] Optimal practice recommendations require estimates of the frequency and nature of adverse events. In the most recent ED ketamine guideline, recommendations are based on data drawn from a 2009 meta-analysis of 8,282 children.[2-4]

Larger ketamine studies would permit more precise estimates of the frequencies of adverse events and would help resolve disagreements between existing studies on the presence and magnitude of risk factors for such adverse events. The Pediatric Sedation Research Consortium (PSRC) is a multicenter registry that has been collecting data since 2004; however, the majority of children in its 2 studies of ketamine received their sedation in non-ED settings.[6,7] Additionally, most of these patients received coadministered propofol or benzodiazepines, further differentiating them from the typical ED format of administering ketamine alone.[6,7]

Importance

A study of ED ketamine as a sole sedative using the PSRC registry would provide the largest available data set to best inform dissociative sedation practice.

Goals of This Investigation

We wished to address 2 questions: When ketamine is administered as a sole sedative for ED pediatric procedures, what are the frequencies of critical and high-risk adverse events? What are the clinical predictors of these adverse events?

MATERIALS AND METHODS

Study Design and Setting

We performed an analysis of the existing PSRC registry between July 1, 2004, and July 1, 2024,

Editor's Capsule Summary

What is already known on this topic

Ketamine is a common emergency department (ED) procedural sedation agent for children.

What question this study addressed

How frequently do critical (life-threatening) or high-risk (requiring immediate intervention) adverse events occur during ED pediatric ketamine sedations?

What this study adds to our knowledge

Over 20 years, there were 69 high-risk adverse events (0.5%; 95% confidence interval 0.4 to 0.7%) in the 12,780 pediatric ED ketamine sedations in a multicenter registry. Hypoventilation requiring treatment predominated. Laryngospasm occurred in 9 patients (<0.1%).

How this is relevant to clinical practice

Significant adverse events from pediatric ED ketamine sedations were uncommon, supporting the safety of ketamine sedation.

adhering to STROBE guidelines. The PSRC is a collaborative research sedation network, with 84 total participating institutions contributing data during all or portions of the study period. PSRC members administer pediatric procedural sedation in various locations, including academic centers, community hospitals, and dental practices (Appendix E1, available online at http://www.annemergmed.com). This secondary analysis study of deidentified data was deemed exempt by the Loma Linda University Institutional Review Board.

The PSRC structure and data collection methodology have been previously described.[6-12] Briefly, sedation practitioners enter their encounter data into a standardized, password-protected, web-based tool. Standard answer sets allow for clear coding and interpretation of responses. The system includes computer code designed to validate data at the time of data entry (preventing logical errors) and branching logic.[8-10] Participating PSRC sites submit more than 90% of their pediatric sedation cases, submit data using a secure portal, and perform recurring 6-month audits.

Selection of Participants

We included ED children (aged less than 18 years) who received ketamine as the sole sedative, ie, excluding those with coadministered propofol, benzodiazepines, or other sedatives.

Measurements

We collected the characteristics of the subjects—age (years), weight (kg), American Society of Anesthesiologists (ASA) physical status, the presence of upper respiratory infection or the diagnosis or high suspicion of obstructive sleep apnea—the primary procedure type, and if opioids were administered during the ED visit.

The PSRC database includes both a legacy phase (from July 1, 2004, to April 26, 2020) and the current phase (from April 27, 2020, to July 1, 2024), with the current phase using more detailed recording. To link both phases for this analysis, we back-coded data from the current phase to comply with the legacy structure.

Outcomes

Our main outcomes were the frequency of critical events and high-risk events (as defined by the PSRC) and their components. Our secondary outcomes were the predictors of critical events and the predictors of either critical or high-risk events.

Critical events (those that are life-threatening and require immediate attention and intervention) include death, cardiac arrest, clinical or radiologic suspicion for pulmonary aspiration, allergic reaction, anaphylaxis, or any event (other than the aforementioned) requiring tracheal intubation, supraglottic or laryngeal mask airway, chest compressions, epinephrine intravenously or intramuscularly, muscle relaxant or paralytic agent, vasopressor intravenously, or rapid response team, code team, or emergency anesthesia consultation.

High-risk events (those that require an advanced level of skill and/or capacity to manage and have potential to become a critical event if untreated) include apnea, complete airway obstruction, laryngospasm, seizure, or any event (other than the aforementioned) requiring bag-mask ventilation, continuous positive airway pressure, positive end-expiratory pressure, oral airway, laryngospasm notch, additional sedative to relieve laryngospasm, atropine, flumazenil, naloxone, or unplanned hospital admission or increase in level of care.

Analyses

We descriptively report the frequencies of adverse events together with their 95% confidence intervals (CIs).

We identified the following candidate predictor variables for our logistic regression analysis based on biological plausibility and prior literature evidence of association with the given adverse event: age (years), ASA physical status, upper respiratory infection, diagnosis or high suspicion of obstructive sleep apnea, and opioids during ED visit. The only missing data were 3.9% of ASA physical status measures, which we replaced using multiple imputation.

For each model, we calculated the area under the receiver operating curve and the Hosmer-Lemeshow goodness-of-fit. To accommodate these data, clustered sandwich standard error estimates, which allowed for intrasite correlation, were used.

We performed all above analyses using Stata 15.1 (StataCorp, College Station, Texas, USA).

RESULTS

Characteristics of Study Subjects

Of the 755,816 total sedation encounters in the database between July 1, 2004, and July 1, 2024, there were 12,780, which met our inclusion and exclusion criteria. Their characteristics are shown in Table 1.

Table 1. Characteristics of study subjects/sedation encounters.

	No. (N=12,780)
Item	**n (%)**
Age (median years, interquartile range)	7 (4, 11)
Age, category	
<6 mo	31 (0.2)
6 to <12 mo	167 (1.3)
1-2 y	1,582 (12.4)
3-5 y	2,646 (20.7)
6-9 y	3,902 (30.5)
10-12 y	2,337 (18.3)
13-17 y	2,117 (16.5)
Weight (median kg, interquartile range)	26 (18, 43)
ASA physical status	
I	11,420 (89.4)
II	802 (6.3)
III	29 (0.23)
IV	34 (0.27)
Missing	495 (3.9)
Upper respiratory infection	17 (0.1)
Primary procedure type	
Orthopedic	6,459 (50.5)
Surgical	2,167 (17.0)
Skin	981 (7.7)
Dental	336 (2.6)
Neuro	114 (0.9)
Oncology	32 (0.3)
Radiology	17 (0.1)
Gastrointestinal	11 (0.1)
Airway	2 (0.02)
Cardiac	1 (0.008)
Other or missing	2,660 (20.8)
Opioids administered during the ED visit*	1,741 (13.6)
Fentanyl	957 (7.5)
Morphine	915 (7.2)
Oxycodone	14 (1.1)
Hydrocodone	11 (0.09)
Hydromorphone	8 (0.06)

ASA, American Society of Anesthesiologists; *ED*, emergency department.
*Some patients received more than one opioid.

Frequency Results

There were 2 children with critical adverse events (0.016%, 95% CI 0.0019 to 0.057) with no reported deaths or permanent sequelae (Table 2).

The first critical event was in a 12-year-old, 55 kg child with ASA II undergoing an orthopedic procedure. There was clinical or radiologic suspicion of pulmonary aspiration, but there was no desaturation, positive pressure ventilation, intubation, unplanned hospitalization, or death. No further details are available.

The second critical event was in a 10-year-old, 48 kg child with an unrecorded ASA and an unrecorded procedure type. There was anaphylaxis associated with apnea, desaturation, positive pressure ventilation, and unplanned hospital admission. There was no intubation or death. The presumed precipitant of the anaphylaxis was not recorded, and no further details are available.

There were 67 children with high-risk events (0.52%, 95% CI 0.41 to 0.66), including 41 occurrences of positive pressure ventilation, 36 of apnea, and 7 of laryngospasm.

Predictor Results

We were unable to model critical adverse events alone, given just 2 occurrences. Predictors of either critical or high-risk adverse events were age more than or equal to 10 years and administered opioids. Higher ASA physical status, upper respiratory infection, and obstructive sleep apnea were not predictive (Table 3).

LIMITATIONS

This study is subject to the limitations expected of a self-reported registry. Sedation practices, regimens, and thresholds for adverse events and interventions no doubt varied between individual practitioners and institutions. We are limited to the data prospectively entered by registry participants and are unable to obtain more detailed information about the adverse events reported.

This study is also subject to the usual limitations of an observational analysis. Although our modeling included the most plausibly related variables, this cannot exclude the possibility of residual confounding. Several of our study variables were infrequent, and therefore, some of the calculations are based on small numbers.

Table 2. Frequency of critical or high-risk adverse events.

Adverse Events	No. (n=12,780)	Percentage (95% CI)
PSRC critical or high-risk events	69	0.54 (0.42 to 0.68)
PSRC critical events*	2	0.016 (0.0019 to 0.057)
Clinical/radiologic suspicion for pulmonary aspiration	1	0.0078 (0.00020 to 0.044)
Anaphylaxis	1	0.0078 (0.00020 to 0.044)
PSRC high-risk events†	67	0.52 (0.41 to 0.66)
Positive pressure ventilation	41	0.32 (0.23 to 0.43)
Apnea	36	0.28 (0.20 to 0.39)
Complete airway obstruction	9	0.070 (0.032 to 0.13)
Laryngospasm	7	0.055 (0.022 to 0.11)
Oral airway	2	0.016 (0.0019 to 0.057)
Unplanned hospital admission / increase in level of care	1	0.0078 (0.00020 to 0.044)

IV, Intravenous.
*Some patients had more than one event. There were no other critical events: death, cardiac arrest, tracheal intubation, supraglottic or laryngeal mask airway, chest compressions, epinephrine IV or intramuscular, muscle relaxant or paralytic agent, vasopressor IV, or rapid response team, code team, or emergency anesthesia consultation.
†Some patients had more than one event. There were no other high-risk events: seizure, laryngospasm notch, additional sedative to relieve laryngospasm, or atropine.

Table 3. Predictors of critical or high-risk adverse events (n=12,780).*

Variables	Adjusted Odds Ratios (95% CI)
Age (y)	
<3	2.71 (0.79, 9.33)
3-5	reference
6-9	2.27 (1.23, 4.20)
10-12	5.03 (3.04, 8.33)
13-17	2.74 (1.62, 4.63)
ASA category	
I	reference
II	1.72 (0.80, 3.70)
III or IV	3.20 (0.89, 11.47)
Upper respiratory infection	1.0†
Diagnosis or high suspicion of obstructive sleep apnea†	1.0†
Opioid during ED visit	3.11 (1.54, 6.26)

ED, Emergency department.
*The area under the receiver operating curve was 0.718 (95% CI 0.657, 0.780), and the Hosmer-Lemeshow goodness-of-fit was *P*=.100.
†There were no occurrences of critical or high-risk adverse events in any subjects with upper respiratory infection or the diagnosis or high suspicion of sleep apnea.

Institutions that comprise the PSRC are self-selected and predominantly provide elective sedations. Contributing sites are typically highly motivated and organized sets of sedation systems, and findings described may not reflect outcomes found in widespread practice.

DISCUSSION

In this study, we report the frequencies and predictors of critical and high-risk adverse events using the largest yet available sample of ketamine administered for ED pediatric procedural sedation. These data strongly validate the safety of dissociative sedation administered by emergency physicians.

One critical event in our sample was a child with clinical or radiologic suspicion of pulmonary aspiration. Given the absence of associated desaturation, positive pressure ventilation, intubation, unplanned hospitalization, or death, however, this occurrence had no apparent sequelae and, thus, was not clinically consequential. Despite decades of continual worldwide use, there are no documented reports of clinically significant aspiration when using ketamine as a primary sedative, except dated reports in compromised neonates.[2,13-15] Indeed, given this track record and this drug's unique maintenance of protective airway reflexes, ketamine would appear to be the sedative of choice when potential aspiration is a specific clinical concern.[2,14]

The second critical event in our sample was a child with anaphylaxis associated with apnea, positive pressure ventilation, and unplanned hospital admission. Ketamine allergy is exceptionally rare, and the precipitating factor in this case is unknown.[16,17]

There is disagreement in the ketamine literature regarding various predictors for adverse events. Although 2 prior studies have found no association with opioids, a third study did find an association.[18-20] We found a significant but modest association, corroborating this latter study in which administration within 30 minutes prior to ketamine appeared to represent the greatest risk.[20] Prior opioids are certainly not a contraindication to ketamine given the ethical imperative to meaningfully address a child's pain, as well as the modest elevation of observed risk. However, coadministration of opioids with ketamine, which is a powerful analgesic, cannot be recommended. When feasible, avoidance of closely spaced administration of opioids prior to ketamine appears prudent.

The impact of upper respiratory infections on sedation risk also remains controversial. Although some sedation studies have identified it as a predictor of adverse events, others have not.[9,18,21-23] Our study corroborates the latter conclusion for ketamine as a sole agent.

As with prior larger ED ketamine studies, we found that older children (eg, aged more than or equal to 10 years) demonstrate a modest increase in adverse events.[3,22,24]

As with prior larger ED ketamine studies, we found no predictive effect of the ASA physical status.[3,22] Further, we found no elevated risk with known or high suspicion of obstructive sleep apnea. These findings are at marked variance, however, with studies of propofol or ketofol sedation in which substantial risk associations are typical.[7,9,25] It is plausible that the ketamine's cardiopulmonary support may better support children with substantial underlying illness and that its unique maintenance of airway muscle tone and spontaneous ventilations mitigates the adverse effect of obstructive sleep apnea and minor airway procedures. As such, when procedural sedation is warranted in these groups, ketamine may be the safest choice.

In summary, this largest yet available study of ketamine as a sole agent for ED pediatric procedural sedation showed a high level of safety and should represent the most reliable estimates of adverse event frequency and risk factors available to advise patient care. We found that critical adverse events were rare and high-risk events uncommon. Modest predictors of these events were age more than or equal to 10 years and administered opioids.

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Data sharing statement: Study data are the property of the Pediatric Sedation Research Consortium and can be available pending Pediatric Sedation Research Consortium Research Committee approval.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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