Predictors of Laryngospasm During 276,832 Episodes of Pediatric Procedural Sedation

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Study objective: Laryngospasm is a rare but potentially life-threatening complication of sedation. The objective of this study was to perform a predictor analysis of biologically plausible predictors and the interventions and outcomes associated with laryngospasm.

Methods: Secondary analysis of prospectively collected data from consecutively sedated patients, less than or equal to 22 years of age, at multiple locations at 64 member institutions of the Pediatric Sedation Research Consortium. The primary outcome was laryngospasm. The independent variables in the multivariable model included American Society of Anesthesiologists category, age, sex, concurrent upper respiratory infection, medication regimen, hospital sedation location, whether the procedure was painful, and whether the procedure involved the airway. The analysis included adjusted odds ratios (aORs) and predicted probabilities.

Results: We analyzed 276,832 sedations with 913 reported events of laryngospasm (overall unadjusted prevalence 3.3:1,000). A younger age, a higher American Society of Anesthesiologists category, a concurrent upper respiratory infection (aOR 3.94, 2.57 to 6.03; predicted probability 12.2/1,000, 6.3/1,000 to 18.0/1,000), and airway procedures (aOR 3.73, 2.33 to 5.98; predicted probability 9.6/1,000, 5.2/1,000 to 13.9/1,000) were associated with increased risk. Compared with propofol alone, propofol combination regimens had increased risk (propofol+ketamine: aOR 2.52, 1.41 to 4.50; predicted probability 7.6/1,000, 3.1/1,000 to 12/1,000; and propofol+dexmedetomidine: aOR 2.10, 1.25 to 3.52; predicted probability 6.3/1,000, 3.7,/1,000 to 8.9/1,000). Among patients with laryngospasm, the resulting outcomes included desaturation less than 70% for more than 30 seconds (19.7%), procedure not completed (10.6%), emergency airway intervention (10.0%), endotracheal intubation (5.3%), unplanned admission/increase in level of care (2.3%), aspiration (1.1%), and cardiac arrest (0.2%).

Conclusion: We found increased associations of laryngospasm in pediatric procedural sedation with multiple biologic factors, procedure types, and medication regimens. However, effect estimates showed that the laryngospasm prevalence remained low, and this should be taken into consideration in sedation decisionmaking. [Ann Emerg Med. 2022;80:485-496.]

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INTRODUCTION

Background

Laryngospasm involves glottic closure and the cessation of ventilation despite the persistence of respiratory effort. Of all sedation-related adverse events, laryngospasm has the highest potential for serious complications, which include hypoxemia, bradycardia, aspiration, and cardiac arrest.[1] The prevalence of and risk factors for laryngospasm have been studied for general anesthesia in the operating room (OR) but are less well established for procedural sedation.

General anesthesia has long been associated with laryngospasm around airway manipulation, including intubation and extubation. Laryngospasm has been studied in patients receiving general anesthesia in the OR, with a prevalence of 17/1,000 in a study of 136,929 adult and pediatric cases collected between 1967 and 1978.[2] A more recent study from 2016, representing modern anesthesia techniques, demonstrated a laryngospasm prevalence of 0.45/1,000 among 49,373 cases.[3] The identified risk factors for laryngospasm among children undergoing general anesthesia include intercurrent upper respiratory infection, active asthma, the presence of an airway anomaly, airway procedures, age less than 3 months, and the use of a laryngeal mask airway.[4]

Procedural sedation, in contrast, rarely involves airway management by endotracheal intubation. Pediatric procedural sedation studies have described a wide range of laryngospasm

Editor's Capsule Summary

What is already known on this topic

Laryngospasm can occur during procedural sedation.

What question this study addressed

What are the predictors and outcomes of sedation-associated laryngospasm in children?

What this study adds to our knowledge

In this multicenter observational study of 276,832 pediatric sedation events there were 913 with laryngospasm. Significant predictors of slightly elevated risk were upper respiratory infection, airway procedure, and the combination of propofol with ketamine. Serious outcomes were rare.

How this is relevant to clinical practice

Although predictors of laryngospasm were identified in this large sample, the absolute magnitude of the effect differences appear too trivial to impact clinical decision making for typical patients.

prevalence.[5-10] Larger studies from 2006 (30,037 sedations) and 2009 (49,836 sedations) found 13 cases of laryngospasm (0.43/1,000), with 1 cardiac arrest, and 96 cases of laryngospasm, with a 2.1/1,000 event rate, respectively.[6,8] A 2016 meta-analysis of emergency department sedations found laryngospasm to be most common with propofol+ketamine.[9]

Importance

Although laryngospasm during sedation is a critical respiratory adverse event, its rare occurrence provides significant challenges for research. Most prior studies have been too small to yield precise estimates of the prevalence of laryngospasm, especially in clinical subgroups, and underpowered to detect potentially important risk factor associations. The ranging prevalence of laryngospasm among prior studies raises the possibility of not only differences in sedation medication regimens and standards of practice but also differences related to the study methodology, operational definition of laryngospasm, and eligibility criteria. It is of particular importance to understand the patient- and procedural-level risk factors as well as the medication regimen–associated risk in order to predict which patients are at increased risk of laryngospasm and to choose the safest and most effective sedation agents.

Goals of This Investigation

We analyzed the largest multicenter database of the pediatric procedural sedation practice with the aim of quantifying an accurate prevalence of laryngospasm and performed a predictor analysis of biologically plausible predictors of laryngospasm.

MATERIALS AND METHODS

Study Design and Setting

This was a secondary analysis of the Pediatric Sedation Research Consortium (PSRC)'s multicenter database. The PSRC is a collaborative research network of sedation providers from 64 institutions. PSRC members provide pediatric procedural sedation in a variety of locations, including free-standing children's hospitals, children's hospitals within academic medical centers, community hospitals, free-standing imaging centers, and dental offices. Each site used its own institutional criteria to determine whether patients were appropriate candidates for pediatric procedural sedation. The sites were mandated to submit more than 90% of pediatric procedural sedation cases performed in the selected area to minimize selection bias. The participating sites are listed in Appendix E1 (available at http://www.annemergmed.com). The PSRC collaboration and the methodology for data collection have been described in a previous study.[6]

Selection of Participants

We included sedations from all sites performed between January 1, 2013, and December 31, 2019, inclusively, for patients less than or equal to 22 years of age. We excluded any case in which the weight was documented as less than 3.6 kg (the average newborn weight), the American Society of Anesthesiologists (ASA) category was missing, or there was no sedation medication recorded. We also excluded cases in which only intramuscular ketamine was used (Figure 1).

Measurements

The patient-level characteristics included age, sex, ASA classification, and the presence of an upper respiratory infection. Patients ranged from ASA class 1 (normal, healthy patients) to class 4 (patients with severe systemic diseases that are constant threats to life).[11] The procedure-level characteristics included the location of sedation (radiology, sedation unit, ED, endoscopy suite, intensive care, or other [which included burn unit, catheterization laboratory, dental suite/office, OR, pediatric floor, pediatric/specialty clinic, and radiation oncology]), provider level of training and specialty, primary procedure, and sedation medications used. The predictor medications included propofol, midazolam, opioids, ketamine, dexmedetomidine, nitrous oxide, and other (which included any single use of pentobarbital, methohexital, chloral hydrate, etomidate, or thiopental, or 33 different combinations in total, each with a prevalence of less than 1%).

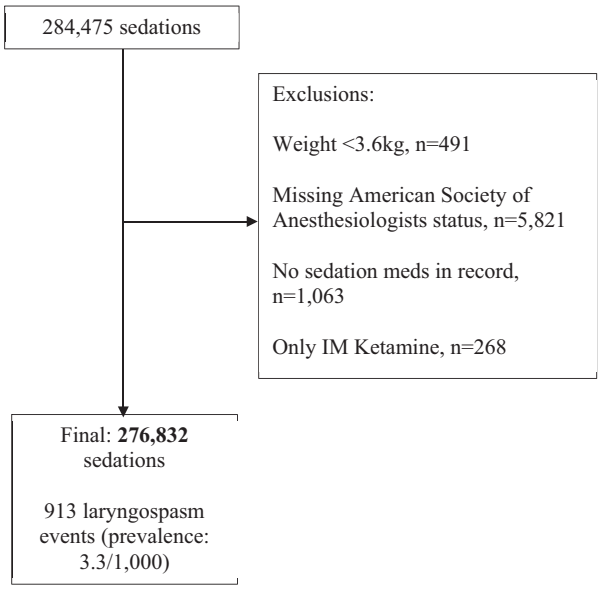

Figure 1. Flow diagram. *Over the years of data collection, centers reported an average of 97% of sedations performed. *IM*, intramuscular.

Outcomes

The primary outcome, laryngospasm, was defined by the PSRC as the "complete or nearly complete lack of air movement with respiratory effort and with or without stridor, not relieved by chin repositioning or oral/nasal airway." This definition was available to the users of the database who entered sedation data. Subsequent laryngospasm outcomes included cardiac arrest, emergency anesthesia consultation, code team involvement, procedure not completed due to complications, emergency airway intervention, and unplanned admission/increase in level of care. Three levels of hypoxemia, all mutually exclusive, were also included as laryngospasm outcomes: 80% to 89%, 70% to 79%, and less than 70%, all lasting more than 30 seconds.

The recorded airway interventions included bag–mask ventilation, continuous positive airway pressure/positive end-expiratory pressure, endotracheal intubation, nasotracheal intubation, administration of a muscle relaxant, jaw thrust/chin lift, nasopharyngeal airway, oral airway, repositioning/neck roll, and supraglottic airway/laryngeal mask airway.

Analysis

Data sources/measurement. A standardized, password-protected, web-based data collection tool, maintained by the Dartmouth Bioinformatics Group, was used for data collection and storage.[6,12-16] The quality of the data was ensured by requiring each institution to identify a primary investigator and agree to the standardized methodology for data collection and quality oversight from the sedation/anesthesia sites at their location. All institutions performed periodic audits of the records to ensure data integrity.

The data collection system asked one question per screen and dynamically generated an interface for each subsequent question based on the response from the previous question. Standard answer sets allowed the clear coding and interpretation of responses. The system included computer code that was designed to validate data at the time of data entry (preventing logical errors) and branching logic.[6,8]

Bias. Each institution was required to perform an audit of the records on a 6-month basis and provide a record of both the total number of cases performed and the number submitted to the database. The PSRC member centers reported an average of 97% of sedations performed each year. Audits of missing records have been determined as random.[17]

Statistical methods. The demographic and clinical factors were described using frequencies and proportions and medians with interquartile ranges for categorical and continuous variables, respectively. The prevalence of laryngospasm was expressed as events per 1,000 cases.

We estimated a multivariable logistic regression model with laryngospasm as the dependent variable and the following independent variables: age, ASA category, presence of an upper respiratory infection, location of procedure and grouping of procedure (airway, painful, other), and medication regimen (coded as a set of indicator variables with propofol as the referent).[4,7,9,13,18,19] Each procedure was defined a priori as "painful" (which included "fracture reduction" or "other painful"), "airway" (which included "airway procedure/bronchoscopy"), "dental," "upper endoscopy," or "all others" (which included all other procedures neither "painful" nor "airway" listed in Table 1). We chose propofol as the referent medication, as it was the most common medication in this data set and, thus, would provide the greatest precision in the analysis. However, we recognize that intravenous ketamine has the lowest prevalence of serious adverse events and most frequent use in ED sedations.[10,18]

In addition to these variables, we also controlled for patient sex, as per previously published studies of laryngospasm risk.[13,16,19,20] These variables were selected based on documented associations with laryngospasm and our expert consensus on the risk factors for laryngospasm during sedation. In order to maximize precision, we did not include the provider specialty, as the preliminary analysis for this study did not show that the provider type was associated with laryngospasm.[12]

We performed 2 sensitivity analyses to further interrogate the data. The first evaluated the risk of laryngospasm with

Table 1. Population characteristics and laryngospasm prevalence (N=276,832).

Variables	No Laryngospasm (%)	Laryngospasm (%)	Unadjusted Prevalence per 1,000
Overall	275,919	913	3.3
Sex			
Female	122,179 (44.3)	413 (45.2)	3.4
Male	153,740 (55.7)	500 (54.8)	3.2
Age, years			
<1	51,715 (18.7)	192 (45.2)	3.7
2-5	95,653 (34.7)	301 (33.0)	3.1
6-9	58,136 (21.1)	206 (22.6)	3.5
10-14	42,472 (15.4)	143 (15.7)	3.4
15-22	27,943 (10.1)	71 (7.8)	2.5
American Society of Anesthesiologists status			
I	60,444 (21.9)	117 (12.8)	1.9
II	168,443 (61.0)	608 (66.6)	3.6
III	45,836 (16.6)	181 (19.8)	3.9
IV	1,196 (0.4)	7 (0.8)	5.8
Concomitant upper respiratory infection	4,796 (1.7)	60 (6.6)	12.4
Primary procedure*			
Radiology (MRI/CT/renal, bone scan, VCUG)	133,967 (48.6)	325 (35.6)	2.4
Oncology (LP/bone marrow)†	60,811 (22.0)	184 (20.2)	3.0
Surgical (minor procedure)‡	28,941 (10.5)	116 (12.7)	4.0
GI (upper/lower endoscopy)	24,421 (8.9)	198 (21.7)	8.0
Other§	19,209 (7.0)	62 (6.8)	3.2
Fracture reduction	7,093 (2.6)	10 (1.1)	1.4
Dental	5,294 (1.9)	42 (4.6)	7.9
Cardiac (catheterization or ECHO)	2,532 (0.9)	2 (0.2)	0.8
Airway procedure/bronchoscopy	634 (0.2)	18 (2.0)	27.6
Neuro (EEG, EMG)	232 (0.1)	0 (0.0)	0
Location of sedation			
Radiology	113,564 (41.2)	272 (29.8)	2.4
Sedation unit	88,657 (32.1)	351 (38.4)	4.0
Other‖	56,482 (20.5)	168 (18.4)	3.0
ED	7,414 (2.7)	13 (1.4)	1.8
Endoscopy suite	6,186 (2.2)	84 (9.2)	13.4
Critical care (ICU/PACU)	3,616 (1.3)	25 (2.7)	6.9
Provider responsible			
Intensivist	155,587 (56.4)	641 (70.2)	4.1
Pediatric emergency physicians	47,749 (17.3)	87 (9.5)	1.8
Subspecialty pediatrician/hospitalist	28,834 (10.5)	60 (6.6)	2.1
Anesthesiologist (including pediatric anesthesiologist)	28,716 (10.4)	115 (12.6)	4.0
PA/NP/RN	8,187 (3.0)	1 (0.1)	0.1
Other¶	5,827 (2.1)	8 (0.9)	1.4
Trainee (any specialty) (fellow/resident)	552 (0.2)	1 (0.1)	1.8
Emergency physician	467 (0.2)	0 (0.0)	0
Medications			
Propofol alone	142,590 (51.7)	397 (43.5)	2.8
Ketamine IV alone	6,653 (2.4)	9 (1.0)	1.4

Table 1. Continued.

Variables	No Laryngospasm (%)	Laryngospasm (%)	Unadjusted Prevalence per 1,000
Dexmedetomidine alone	5,982 (2.2)	0 (0.0)	0
Midazolam alone	5,673 (2.1)	0 (0.0)	0
Nitrous oxide alone	4,616 (1.7)	1 (0.1)	0.2
Other single medication alone[#]	1,976 (0.7)	3 (0.3)	1.5
Other inhaled alone	853 (0.3)	3 (0.3)	3.5
Combination medications			
Propofol+opioid	39,039 (14.1)	185 (20.3)	4.7
Propofol+midazolam	14,548 (5.3)	52 (5.7)	3.6
Other combinations[**]	22,377 (8.1)	145 (15.9)	6.5
Propofol+midazolam+opioid	7,389 (2.7)	45 (4.9)	6.1
Midazolam+dexmedetomidine	6,699 (2.4)	0 (0.0)	0
Ketofol	6,034 (2.2)	40 (4.4)	6.6
Propofol+dexmedetomidine	4,990 (1.8)	29 (3.2)	5.8
IV ketamine+midazolam	3,856 (1.4)	4 (0.4)	1.0
Midazolam+opioid	2,644 (1.0)	0 (0.0)	0

CT, computed tomography; *ECHO*, echocardiogram; *EEG*, electroencephalogram; *EMG*, electromyography; *GI*, gastroenterology; *IV*, intravenous; *LP*, lumbar puncture; *MRI*, magnetic resonance imaging; *NP*, nurse practitioner; *PA*, physician assistant; *PACU*, postanesthesia care unit; *RN*, registered nurse; *VCUG*, voiding cystourethrogram.
*Some patients had more than 1 procedure; total procedures=284,091.
Primary procedure:
†Oncology: lumbar puncture (LP) diagnostic, LP chemo and bone marrow, radiation.
‡Surgical: botox, joint injection, ortho other, other painful, renal biopsy.
§Other: auditory brainstem response, casting, examination under anesthesia, ophthalmology, other nonpainful, peripherally inserted central catheter.
Location of sedation:
‖Other=Burn unit, catheterization laboratory, dental suite/office, OR, pediatric floor, pediatric/specialty clinic, radiation oncology, other.
Provider responsible:
¶Other=radiologist, dentist, other.
#Other single medication alone=pentobarbital, methohexital, chloral hydrate, etomidate, or thiopental.
**Other Combinations=Any other combination of 2 or more medication regimens (33 different combinations in total) not otherwise specified and each with prevalence of more than 1%. The 2 most common combinations, which lead to 25 cases of laryngospasm each, were propofol+nitrous oxide+other potent inhaled agent and propofol+IV ketamine+opioid.

severe outcomes (hypoxia <70% for >30 seconds, use of a muscle relaxant, emergency airway intervention, endotracheal intubation, or cardiac arrest), and the second looked at ED-similar settings (ED, radiology, pediatric floor, pediatric/subspecialty clinic) and excluded more ill patients (ASA category III, IV). Adjusted odds ratios (aORs) with 95% confidence intervals (95% CIs) were determined. The predicted probabilities, with 95% CIs, were calculated from the model to help better understand the magnitude of the effect. The area under the receiver operating curve and the Hosmer-Lemeshow goodness-of-fit test were used to evaluate the overall model fit. The number needed to harm was calculated by multiplying the aOR of the independent variable to determine an estimated probability, minus the base rate to determine the absolute risk difference with its 95% CIs. Given that these data included multiple observations from each site, the assumption of independent observations may not have held. To accommodate these data, clustered sandwich standard error estimates, which allowed for intrasite correlation, were used. The statistical analysis was performed using Stata IC version 16.1 (Stata Corp). This study was approved by the Boston Children's Hospital Institutional Review Board.

RESULTS

Characteristics of Study Subjects

In total, 276,832 sedations were analyzed over the 7-year period. The population and provider characteristics, procedures performed, locations of sedation, and medications used are provided in Table 1.

Main Results

Nine hundred and thirteen children developed laryngospasm, with an overall unadjusted prevalence of 3.3/1,000. Eight hundred and seventy patients (95.3% of all laryngospasm events) had 1 episode of laryngospasm each; 42 (4.6%) had 2 episodes each; and 1 patient had 3 episodes of laryngospasm during the procedure. In those who had 1 episode of laryngospasm, 135 (14.8%) occurred

before the procedure, 670 (73.4%) occurred during the procedure, and 65 (7.1%) occurred after the procedure. Twenty-eight of the 42 procedures with 2 laryngospasm events occurred during and after the procedure.

Unadjusted Results

In decreasing order of frequency, the most common unadjusted prevalences were airway procedure/bronchoscopy, endoscopy suite, concomitant upper respiratory infection, upper/lower endoscopy, and dental procedure. Among the sedation regimens that were used in at least 1% of children, intravenous ketamine had the second-lowest unadjusted prevalence, at 1.4/1,000. There were no reported laryngospasm events with midazolam, dexmedetomidine, the combination of midazolam and dexmedetomidine, or the combination of midazolam and an opioid. The unadjusted prevalences were highest with combination medications (propofol+ketamine (ketofol), 6.6/1,000; propofol+midazolam+opioid, 6.1/1,000; and propofol+dexmedetomidine, 5.8/1000; Table 1).

Multivariable Results

The area under the receiver operating curve for the multivariable model and the Hosmer-Lemeshow goodness-of-fit test were not statistically significant, indicating that the model fit reasonably well. The statistically significant patient and procedure predictors for laryngospasm included increased ASA class, younger age, concomitant upper respiratory infection, and airway procedures (Table 2, Figure 2).

Compared to propofol alone, intravenous ketamine alone had a similar odds ratio for laryngospasm (aOR 0.57; 95% CI 0.29 to 1.10) and a comparable predicted probability (ketamine: 1.7/1,000, 95% CI 0.6 to 2.8; propofol: 3/1,000, 95% CI 2.2 to 3.9; Figure 3). Two propofol combination regimens had increased odds for laryngospasm compared to propofol alone. These included ketofol (aOR 2.52, 95% CI 1.41 to 4.50; predicted probability 7.6/1,000, 95% CI 3.1/1,000 to 12/1,000) and propofol+dexmedetomidine (aOR 2.10, 95% CI 1.25 to 3.52; predicted probability 6.3/1,000, 95% CI 3.7/1,000 to 8.9/1,000). This is in contrast to other propofol combination regimens, which did not statistically differ from propofol alone (Table 2, Figure 2).

Number-needed-to-harm calculations with 95% CIs for significant associations included upper respiratory infection (103, 60 to 193); airway procedure (111, 61 to 228); ketofol (199, 87 to 739), and propofol+dexmedetomidine (275, 120 to 1,212; Figure E1, available at https://www.annemergmed.com).

The first sensitivity analysis evaluated instances of laryngospasm with serious outcomes. Increased odds of laryngospasm with serious outcomes were associated with increased ASA class, younger age, concomitant upper respiratory infection, airway procedure, and the use of ketofol. Propofol+opioid became statistically significant; however, propofol+dexmedetomidine was no longer significant. Information regarding aORs and predicted probabilities can be found in Table E1 (available at https://www.annemergmed.com).

The second sensitivity analysis was on procedural sedations performed in ED-similar settings and excluded more ill patients (ASA class III, IV); it showed that the odds of laryngospasm did not differ across these locations. Other predictors, including concomitant upper respiratory infection, American Society of Anesthesiologists classification, younger age, and airway procedure, remained similar. Painful procedures became a positive predictor. Although ketofol remained significant, regimens that became significant included propofol with an opioid and propofol+midazolam+opioid. Propofol+dexmedetomidine was no longer statistically significant. Information regarding aORs and predicted probabilities can be found in Table E2 (available at https://www.annemergmed.com).

Laryngospasm Interventions and Outcomes

The most common airway interventions were jaw thrust/chin lift (73.9% of cases), bag–mask ventilation (54.3%), and continuous positive airway pressure (33.5%). There were 49 endotracheal intubations (5.4%); 7 nasotracheal intubations (0.8%); 14 uses of muscle relaxants, including rocuronium, succinylcholine, and vecuronium (1.5%); and 2 uses of a reversal agent (flumazenil; Table 3).

Subsequent laryngospasm outcomes occurred in 54.4% of cases, with desaturation/hypoxia less than 70% for more than 30 seconds being the most prevalent (180 cases, 19.7%); cardiac arrest occurred in 2 cases (0.2%), and no deaths occurred (Table 4). The 2 cases of cardiac arrest both had primary cardiovascular problems, categorized as ASA class 2, and included a 6-year old undergoing a cardiac procedure with a multiple combination regimen and a 5-year old, who had an upper respiratory infection, undergoing an echocardiogram with propofol with dexmedetomidine.

LIMITATIONS

Our study has several limitations due to the nature of the database. There were no data on why specific medications were chosen for the sedations and no timing or

Table 2. Association model for laryngospasm (N=276,832).

Variables	aORs	95% CI	Predicted Probability (Rate per 1,000)	PP 95% CI
Male	0.99	0.85-1.14	3.3	2.5-4.1
Age (years)				
<1	1.31	0.98-1.75	4.7	3.5-6.0
2-5		Referent	3.6	2.3-4.9
6-9	0.99	0.78-1.24	3.6	2.5-4.6
10-14	0.73*	0.53-0.99	2.6	1.9-3.4
15-22	0.47*	0.29-0.74	1.7	1.2-2.2
American Society of Anesthesiologists category				
I	0.55*	0.40-0.76	1.9	2.6-4.3
II		Referent	3.5	2.6-4.3
III	1.31	0.91-1.87	4.5	2.7-6.3
IV	1.86	0.95-3.63	6.4	2.2-10.6
Concomitant upper respiratory infection	3.94*	2.57-6.03	12.2	6.3-18.0
Procedure				
All others†		Referent	2.6	1.8-3.4
Painful‡	1.48	0.86-2.55	3.8	2.2-5.5
Airway§	3.73*	2.33-5.98	9.6	5.2-13.9
Location				
Radiology		Referent	2.8	1.7-3.9
Sedation unit	1.21	0.75-1.97	3.5	2.1-4.8
Other‖	0.98	0.60-1.61	2.8	1.8-3.7
ED	1.29	0.53-3.19	3.7	0.8-6.6
Endoscopy unit	2.43*	1.27-4.65	6.9	4.2-9.5
Critical care (ICU/PACU)	2.41*	1.27-4.56	6.8	2.8-10.8
Medication				
Propofol alone		Referent	3.0	2.2-3.9
Ketamine IV alone	0.57	0.29-1.10	1.7	0.6-2.8
Nitrous oxide alone	0.10*	0.02-0.60	0.3	−0.2 to 0.8
Propofol+opioid	1.23	0.70-2.17	3.7	1.7-5.8
Propofol+midazolam	1.18	0.67-2.07	3.6	1.6-5.5
Propofol+midazolam+opioid	1.03	0.52-2.05	3.1	1.2-5.1
Ketofol	2.52*	1.41-4.50	7.6	3.1-12.0
Propofol+dexmedetomidine	2.10*	1.25-3.52	6.3	3.7-8.9
IV ketamine+midazolam	0.37	0.07-2.05	1.1	−0.8 to 3.0
Other¶	1.12	0.71-1.75	3.4	2.0-4.8

Analyses adjusted for the following covariates: American Society of Anesthesiologists category, sex, age, hospital location of sedation, medications used, and type of procedure.
Area under the receiver operating curve (95% CI) 0.68 (0.66-0.70).
Hosmer-Lemeshow goodness-of-fit (χ^2=11.02, *P*=.20).
*Statistical significance <0.05.
†All others=all other procedures neither "painful" nor "airway" listed in Table 1
‡Painful=fracture reduction or "other painful."
§Airway=airway procedure/bronchoscopy, dental, or upper endoscopy.
‖Other=Burn unit, catheterization laboratory, dental suite/office, OR, pediatric floor, pediatric/specialty clinic, radiation oncology, other.
¶Other medication regimens that have a prevalence <1% of the total cohort.

dosing data for medications. We did not have data that allowed us to control for site-to-site variability, such as clinical indication, medication use restriction, provider preference, experience, or comfort. In addition, the largest proportion of sedations in this data set (41%) were performed in radiology departments. These sedations are less likely to use analgesia-oriented medications (eg, opioids or ketamine). However, many radiology sedation services

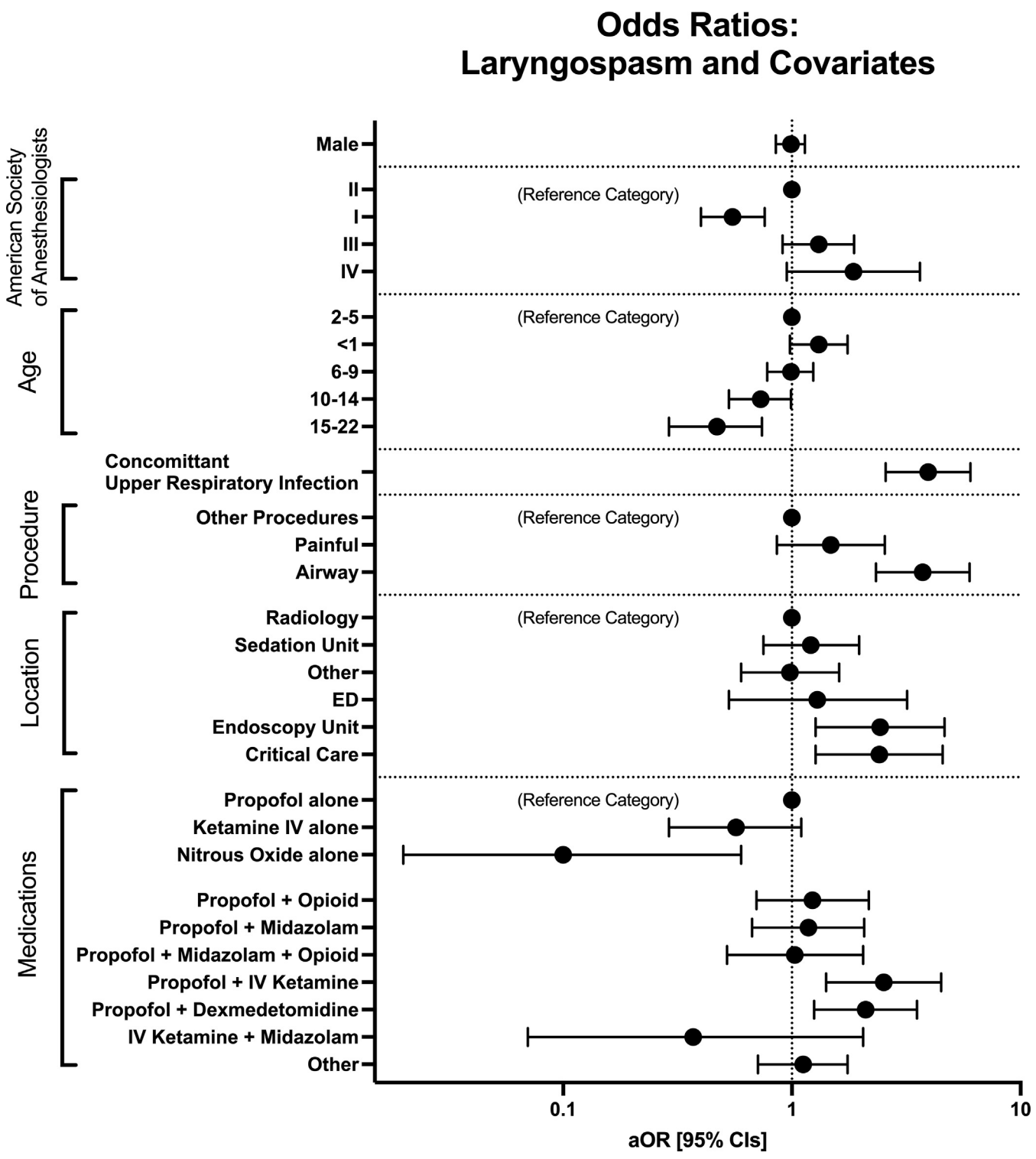

Figure 2. Laryngospasm and covariates: aORs with 95% CIs. *IM*, intramuscular.

are also run by pediatric emergency physicians and, thus, remain highly relevant to the analysis. Although we adjusted for a number of covariates, there may have been unmeasured factors that resulted in the residual confounding of our results.

The practice of deepening the level of sedation for the management of laryngospasm is common, but these data were not available. The variable "emergency airway intervention" did not encompass a predefined set of specific interventions and could have been open to

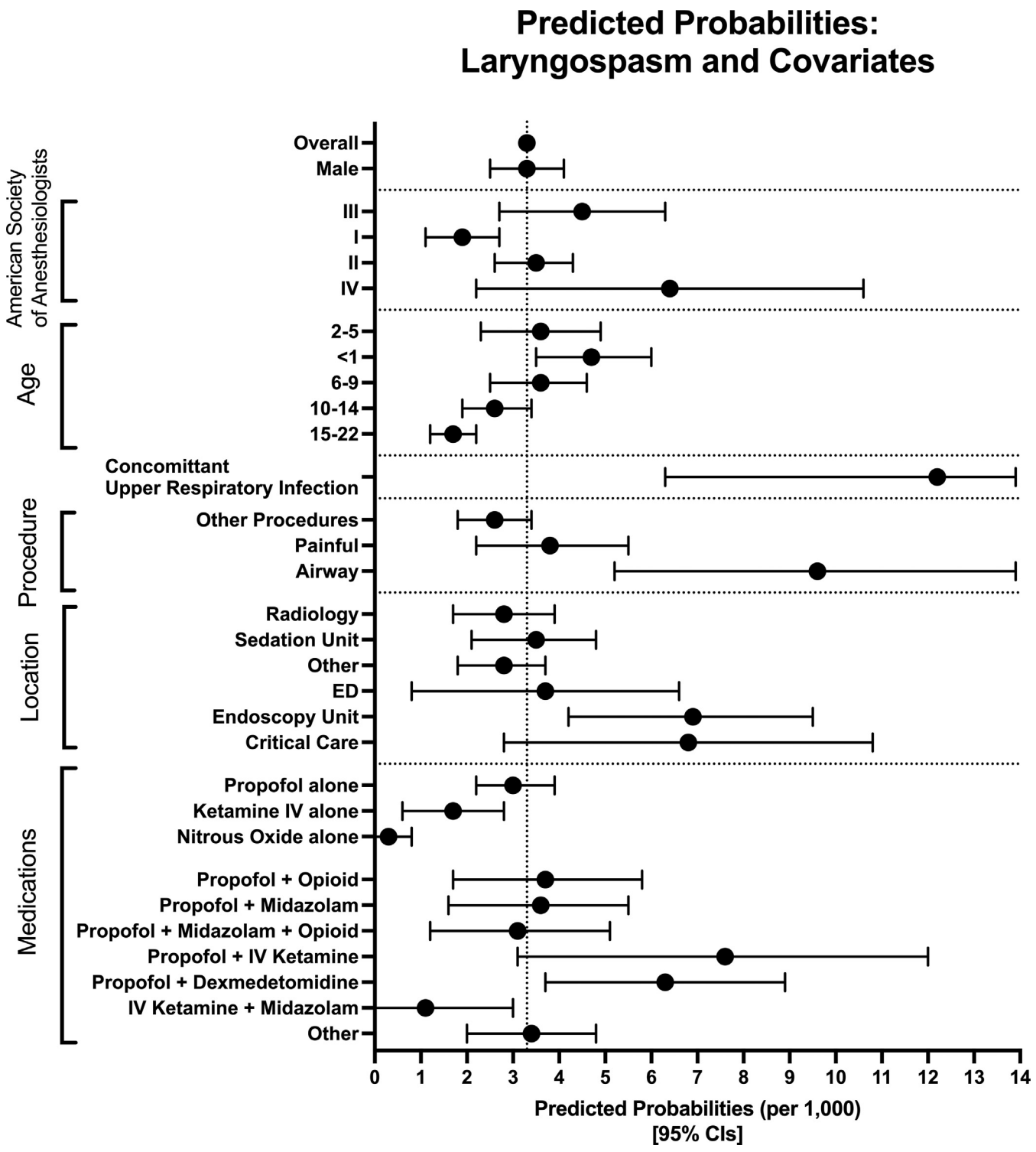

Figure 3. Laryngospasm and covariates: predicted probabilities with 95% CIs. *IV*, intravenous

interpretation, including the use of varying interventions not specifically listed, such as the laryngospasm notch maneuver or intubation, although intubation is a variable separate from "emergency airway intervention" and, therefore, was analyzed.[21] With the nature of data collected across a large group of institutions, there was a possibility that some of the recorded "laryngospasm" events could have been upper airway obstructions and not true instances of laryngospasm. Although laryngospasm should, by definition, involve the complete

Table 3. Airway interventions for laryngospasm cases.*

Variables	N = 913
Jaw thrust/chin lift (%)	675 (73.9)
Repositioning/neck roll (%)	523 (57.2)
BMV (%)	496 (54.3)
CPAP/PEEP (%)	306 (33.5)
Oral airway (%)	137 (15.0)
Nasopharyngeal airway (%)	92 (10.1)
Endotracheal intubation (%)	49 (5.4)
Supraglottic/LMA (%)	43 (4.7)
Muscle relaxant† (%)	14 (1.5)
Nasotracheal tube (%)	7 (0.8)
Reversal agent (flumazenil) (%)	2 (0.2)

BMV, Bag–mask ventilation; *CPAP*, continuous positive airway pressure; *PEEP*, positive end-expiratory pressure; *LMA*, laryngeal mask airway.
*More than one airway intervention may have occurred with a given patient.
†Rocuronium, vecuronium, or succinylcholine.

cessation of air movement, it is possible that some providers checked "laryngospasm" when, in fact, there was some air movement; this would be considered "partial laryngospasm," but this was not captured in the database.

DISCUSSION

To our knowledge, this is the largest study to evaluate the prevalence of and risk factors for laryngospasm during pediatric procedural sedation. The overall laryngospasm prevalence of 3.3/1,000 and the increased risk with certain propofol combination regimens, as well as the increased risks associated with higher ASA status, younger age, presence of upper respiratory infection, and airway procedures, speaks to the importance of medication selection, monitoring, and management during procedural sedation. The strongest nonmedication associations were the presence of an upper respiratory infection, ASA class IV, and airway procedures. Although statistically significant, our effect estimates showed that these absolute rates remained small, with the most significant factor being upper respiratory infection, with a predicted probability of 12.2/1,000. However, given its wide confidence margins, the true value may sit within its 95% CI boundaries, giving a range of 6.3/1,000 to 18/1,000. The number needed to harm suggested that 1 additional case of laryngospasm above baseline would occur for every 103 sedations of patients with upper respiratory infections. However, the true upper respiratory infection number-needed-to-harm value may range from 60 to 193 due to its wide 95% CI boundaries.

Table 4. Laryngospasm outcomes.*

Variables	N = 913
Desaturation/hypoxia <70% for >30 seconds (%)†	180 (19.7)
Desaturation/hypoxia 80%-89% for >30 seconds (%)†	141 (15.4)
Desaturation/hypoxia 70%-79% for >30 seconds (%)†	118 (12.9)
Procedure not completed due to complications (%)	97 (10.6)
Emergency airway intervention (%)	91 (10.0)
Endotracheal intubation (%)	49 (5.4)
Unplanned admission/increase in level of care (%)	21 (2.3)
Emergency anesthesia or code team called (%)	12 (1.3)
Aspiration (%)	10 (1.1)
Cardiac arrest (%)	2 (0.2)
Death (%)	0
Any (%)	497 (54.4)

*More than one subsequent laryngospasm outcome may have occurred with a given patient.
†Desaturation/hypoxia levels are mutually exclusive.

Our finding of a higher prevalence of laryngospasm with certain propofol combination regimens, especially ketofol, is consistent with recent data showing a higher prevalence of adverse events with this regimen.[10] We also described an increased risk of laryngospasm with propofol+dexmedetomidine, in contrast to other combination regimens with propofol. However, the predicted probabilities of laryngospasm remained small, even with these variable associations (ketofol 7.6/1,000; propofol+dexmedetomidine 6.3/1,000; compared to the overall 3.3/1,000 prevalence). For an additional event of laryngospasm above baseline rates, one would need to perform 199 ketofol sedations (95% CI number-needed-to-harm limits 87 to 739) and, respectively, 275 sedations with propofol+dexmedetomidine (95% CI number-needed-to-harm limits 120 to 1,212).

In both sensitivity analyses, the nonmedication associations of upper respiratory infection, younger age, ASA level, and airway procedure all remained statistically significant. In ED-similar populations, painful procedures were also associated with laryngospasm. In both sensitivity analyses, ketofol remained a predictor; however, propofol+dexmedetomidine was no longer predictive, and other propofol combination regimens demonstrated increased risk.

Prior studies describing laryngospasm in pediatric procedural sedation are summarized in Table E3 (available at https://www.annemergmed.com) A 2017 multicenter prospective cohort study of ED procedural sedation found a higher prevalence of serious adverse events with propofol alone compared to intravenous ketamine.[10] These events were primarily apnea, and the study captured only 4 cases of laryngospasm. The rates of laryngospasm during intravenous ketamine alone and propofol alone were not

statistically different. This further adds to the safety profile of the use of intravenous ketamine alone in pediatric procedural sedation as the medication regimen with one of the lowest laryngospasm prevalences (1.4/1,000). These results are in contrast to those of a 2016 meta-analysis of ED procedural sedation, which found that laryngospasm occurred most frequently with ketamine use.[9]

Laryngospasm has multiple potential side effects, including hypoxia, but, as demonstrated in this study, laryngospasm can be well managed, with a very low prevalence of serious complications. However, even a laryngospasm prevalence of 1.4 per 1,000 for intravenous ketamine is high enough to define a need for expertise in airway management; this need especially increases for sedations of higher-risk patients, higher-risk procedures, and those utilizing the identified propofol combination regimens. Among laryngospasm events, desaturation was the most common complication, with 2 cases progressing to cardiac arrest, whereas the remainder had the cessation of laryngospasm and full recoveries.

We found a range of common airway interventions used for the management of laryngospasm with low prevalence of serious complications or poor subsequent laryngospasm outcomes, suggesting that within this data set of sedations performed by dedicated sedation providers, laryngospasm can be effectively managed by a range of providers. This offers further evidence as to the overall safety of pediatric procedural sedation in the hands of dedicated sedation providers who are appropriately trained to effectively recognize and manage adverse events and prevent serious complications. It is important to note that the majority of these sedations were performed by sedation services, in controlled conditions, by providers who provide sedation for hundreds to thousands of procedures per year. This performance reflects that practice and is likely a further argument for the formation of these teams.

Our study identified both biologically plausible predictors of laryngospasm that concurred with existing literature (presence of an upper respiratory infection, younger patients, airway procedures, and more medically complex patients) and medication regimens associated with higher prevalences of laryngospasm.[1,19,22] This is particularly important to emergency physicians, as the use of ketofol to provide procedural sedation has become more common in the emergency setting.[18,22]

Our data indicate that laryngospasm is a rare sedation-related adverse event with an overall prevalence of 3.3/1,000 in pediatric procedural sedations. The risk factors include increasing ASA status, the presence of an upper respiratory infection, younger age, and airway procedures, in addition to propofol combination regimens that include either ketamine or dexmedetomidine. However, our effect estimates show that the absolute occurrence of laryngospasm, even with these associations, is still rare. Number-needed-to-harm calculations show that even for the highest-risk associations (upper respiratory infection and airway procedure), more than 100 sedations are needed to lead to 1 more case of laryngospasm. Our data show a very low risk of serious negative outcomes, highlighting the effective management of laryngospasm by those involved in PSRC data collection. Sedation providers should be aware of the risk factors for laryngospasm when making decisions concerning sedation strategies.

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REFERENCES

1. Visvanathan T, Kluger MT, Webb RK, et al. Crisis management during anaesthesia: laryngospasm. *Qual Saf Health Care*. 2005;14:e3.
2. Olsson GL, Hallen B. Laryngospasm during anaesthesia. A computer-aided incidence study in 136,929 patients. *Acta Anaesthesiol Scand*. 1984;28:567-575.
3. Lee JH, Kim EK, Song IK, et al. Critical incidents, including cardiac arrest, associated with pediatric anesthesia at a tertiary teaching children's hospital. *Paediatr Anaesth*. 2016;26:409-417.
4. Flick RP, Wilder RT, Pieper SF, et al. Risk factors for laryngospasm in children during general anesthesia. *Paediatr Anaesth*. 2008;18:289-296.
5. Peña BM, Krauss B. Adverse events of procedural sedation and analgesia in a pediatric emergency department. *Ann Emerg Med*. 1999;34:483-491.
6. Cravero JP, Blike GT, Beach M, et al. Incidence and nature of adverse events during pediatric sedation/anesthesia for procedures outside the operating room: report from the Pediatric Sedation Research Consortium. *Pediatrics*. 2006;118:1087-1096.
7. Green SM, Roback MG, Krauss B, et al. Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: an individual-patient data meta-analysis of 8,282 children. *Ann Emerg Med*. 2009;54:158-168;e1-e4.
8. Cravero JP, Beach ML, Blike GT, et al. The incidence and nature of adverse events during pediatric sedation/anesthesia with propofol for procedures outside the operating room: a report from the Pediatric Sedation Research Consortium. *Anesth Analg*. 2009;108:795-804.
9. Bellolio MF, Puls HA, Anderson JL, et al. Incidence of adverse events in paediatric procedural sedation in the emergency department: a systematic review and meta-analysis. *BMJ Open*. 2016;6:e011384.
10. Bhatt M, Johnson DW, Chan J, et al. Risk factors for adverse events in emergency department procedural sedation for children. *JAMA Pediatr*. 2017;171:957-964.
11. Mayhew D, Mendonca V, Murthy BVS. A review of ASA physical status–historical perspectives and modern developments. *Anaesthesia*. 2019;74:373-379.
12. Couloures KG, Beach M, Cravero JP, et al. Impact of provider specialty on pediatric procedural sedation complication rates. *Pediatrics*. 2011;127:e1154-e1160.
13. Hertzog JH, Preisberga K, Penfil S. The incidence and nature of allergic and anaphylactic reactions during pediatric procedural sedation: a report from the Pediatric Sedation Research Consortium. *Hosp Pediatr*. 2019;9:16-23.
14. Sulton C, Kamat P, Mallory M, et al. The use of intranasal dexmedetomidine and midazolam for sedated magnetic resonance imaging in children: a report from the Pediatric Sedation Research Consortium. *Pediatr Emerg Care*. 2020;36:138-142.
15. Beach ML, Cohen DM, Gallagher SM, et al. Major adverse events and relationship to nil per os status in pediatric sedation/anesthesia outside the operating room: a report of the Pediatric Sedation Research Consortium. *Anesthesiology*. 2016;124:80-88.
16. Mallory MD, Baxter AL, Yanosky DJ, et al. Emergency physician-administered propofol sedation: a report on 25,433 sedations from the pediatric sedation research consortium. *Ann Emerg Med*. 2011;57:462-468.e1.
17. Research: Pediatric Sedation Research Consortium. Society for Pediatric Sedation. Accessed August 18, 2021. https://pedsedation.org/resources/research/
18. Miller AF, Monuteaux MC, Bourgeois FT, et al. Variation in pediatric procedural sedations across children's hospital emergency departments. *Hosp Pediatr*. 2018;8:36-43.
19. Kamat PP, McCracken CE, Simon HK, et al. Trends in outpatient procedural sedation: 2007-2018. *Pediatrics*. 2020;145:e20193559.
20. Mallory MD, Travers C, McCracken CE, et al. Upper respiratory infections and airway adverse events in pediatric procedural sedation. *Pediatrics*. 2017;140:e20170009.
21. Larson CP Jr. Laryngospasm–the best treatment. *Anesthesiology*. 1998;89:1293-1294.
22. Willman EV, Andolfatto G. A prospective evaluation of "ketofol" (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. *Ann Emerg Med*. 2007;49:23-30.