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Risk Factors for Adverse Events in Emergency Department Procedural Sedation for Children

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IMPORTANCE Procedural sedation for children undergoing painful procedures is standard practice in emergency departments worldwide. Previous studies of emergency department sedation are limited by their single-center design and are underpowered to identify risk factors for serious adverse events (SAEs), thereby limiting their influence on sedation practice and patient outcomes.

OBJECTIVE To examine the incidence and risk factors associated with sedation-related SAEs.

DESIGN, SETTING, AND PARTICIPANTS This prospective, multicenter, observational cohort study was conducted in 6 pediatric emergency departments in Canada between July 10, 2010, and February 28, 2015. Children 18 years or younger who received sedation for a painful emergency department procedure were enrolled in the study. Of the 9657 patients eligible for inclusion, 6760 (70.0%) were enrolled and 6295 (65.1%) were included in the final analysis.

EXPOSURES The primary risk factor was receipt of sedation medication. The secondary risk factors were demographic characteristics, preprocedural medications and fasting status, current or underlying health risks, and procedure type.

MAIN OUTCOMES AND MEASURES Four outcomes were examined: SAEs, significant interventions performed in response to an adverse event, oxygen desaturation, and vomiting.

RESULTS Of the 6295 children included in this study, 4190 (66.6%) were male and the mean (SD) age was 8.0 (4.6) years. Adverse events occurred in 736 patients (11.7%; 95% CI, 6.4%-16.9%). Oxygen desaturation (353 patients [5.6%]) and vomiting (328 [5.2%]) were the most common of these adverse events. There were 69 SAEs (1.1%; 95% CI, 0.5%-1.7%), and 86 patients (1.4%; 95% CI, 0.7%-2.1%) had a significant intervention. Use of ketamine hydrochloride alone resulted in the lowest incidence of SAEs (17 [0.4%]) and significant interventions (37 [0.9%]). The incidence of adverse sedation outcomes varied significantly with the type of sedation medication. Compared with ketamine alone, propofol alone (3.7%; odds ratio [OR], 5.6; 95% CI, 2.3-13.1) and the combinations of ketamine and fentanyl citrate (3.2%; OR, 6.5; 95% CI, 2.5-15.2) and ketamine and propofol (2.1%; OR, 4.4; 95% CI, 2.3-8.7) had the highest incidence of SAEs. The combinations of ketamine and fentanyl (4.1%; OR, 4.0; 95% CI, 1.8-8.1) and ketamine and propofol (2.5%; OR, 2.2; 95% CI, 1.2-3.8) had the highest incidence of significant interventions.

CONCLUSIONS AND RELEVANCE The incidence of adverse sedation outcomes varied significantly with type of sedation medication. Use of ketamine only was associated with the best outcomes, resulting in significantly fewer SAEs and interventions than ketamine combined with propofol or fentanyl.

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Supplemental content

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Procedural pain and anxiety relief is an ethical imperative in the treatment of children given that children have short- and long-term physical, physiological, and psychological effects due to untreated pain.[1-3] As such, *procedural sedation*, defined as the administration of medications to minimize pain and awareness, has become standard practice in pediatric emergency departments (EDs) worldwide to facilitate procedures, such as orthopedic reduction and complex laceration repairs.[4-8] Although ED sedation is regarded as safe, it has been associated with serious adverse events (SAEs).[6,9] The incidence of SAEs has been difficult to determine because of their infrequent occurrence and the lack of large, multicenter surveillance studies focused on systematic detection of adverse events. Previous ED sedation studies, limited by single-center design and small sample sizes, have not been able to reliably associate their use with sedation-related adverse events, their severity, or their outcomes for patients.[9-12]

To improve understanding of the safety and comparative effectiveness of ED procedural sedation, we conducted a large multicenter cohort study using standardized outcome measures that are valid and relevant to clinical practice. Our primary objective was to examine the incidence of sedation-related adverse events and identify risk factors associated with these events. Our secondary objectives were (1) to examine the association of ketamine hydrochloride dose with adverse events and (2) to describe the variation in duration of sedation and ED length of stay (LOS) across categories of sedation medications.

Key Points

Question What practices lead to the best outcomes in children undergoing emergency department procedural sedation?

Findings In this multicenter cohort study of 6295 children undergoing procedural sedation for painful procedures in emergency departments, administration of ketamine hydrochloride as a single agent for sedation had the best outcomes. The addition of propofol or fentanyl citrate to ketamine increased the rates of serious adverse events and significant interventions.

Meaning In the hands of emergency department physicians, procedural sedation for children is safe; sedation achieved using ketamine only was associated with the fewest serious adverse events and interventions.

Methods

We conducted a multicenter prospective cohort study in 6 tertiary care pediatric EDs in Canada from July 10, 2010, to February 28, 2015, in a staged roll-out. All sites are members of the Sedation Safety Study Group of Pediatric Emergency Research Canada, a national collaborative research network.[13] This study received approval from the research ethics board at each participating institution—specifically, IWK Health Center, Halifax, Nova Scotia; Montreal Children's Hospital, Montreal, Quebec; Children's Hospital of Eastern Ontario, Ottawa, Ontario; The Hospital for Sick Children, Toronto, Ontario; Stollery Children's Hospital, Edmonton, Alberta; and Alberta Children's Hospital, Calgary, Alberta. Verbal or written patient informed consent, according to site-specific regulations, was obtained from parents or guardians, and assent was obtained from children 7 years or older.

Study Setting and Population

Children 18 years or younger who underwent parenteral procedural sedation performed by ED physicians for painful procedures were eligible for enrollment. Children were excluded if they received a drug purely for anxiolysis or analgesia without the intent of sedation, if there was a language barrier, or both.

Study Protocol

All procedural sedations were documented using a site-specific electronic sedation form created for study purposes as described in our published protocol.[14] The electronic form (created with Microsoft InfoPath 2007 software; Microsoft Corp) contained all documentation for study and clinical purposes and was completed by the health care professional caring for the child. If a patient declined participation or was not approached for enrollment, electronic sedation documentation continued but program logic prevented study information from being saved to the database. Documentation of study data was standardized to increase efficiency and data quality. A complete list of data fields collected is included in the published protocol.[14] All professionals documenting sedation encounters received standardized training before study initiation.[14] The specifics related to each sedation, including choice of sedation medication and dose, were left to the treating physician.

Estimation of Missed, Eligible Patients

To estimate the proportion of sedations not captured at each site, surveillance for missed, eligible patients was performed for 7 days during the third week of each month. We extrapolated monthly numbers to estimate overall compliance or consent rates because daily surveillance was not feasible at all sites for the study duration. A medical record review of missed patients was performed to determine their age, sex, sedation medication, and adverse event occurrence. Methods to identify missed patients varied by site. Daily hand searching of ED medical records, pharmacy record queries, and electronic medication dispensing system queries were performed depending on which method was available and proved to be the most reliable at each institution. Clinical staff caring for patients were not aware of the surveillance schedule.

Definitions

Standardized definitions from the Quebec Guidelines, a consensus-based document developed by North American experts in pediatric procedural sedation, were used for time intervals and adverse events.[15] These intervention-based definitions represent standardized definitions for outcomes in procedural sedation and outline uniform data collection for clinically important events while minimizing the recording of events for which the significance is difficult to interpret.[16] They

require both the specific clinical event to have occurred and 1 or more appropriate interventions to be performed with the intention of treating or managing it. Specific definitions from the Quebec Guidelines for adverse events measured in this study are documented in eTable 1 in the Supplement. A *successful sedation* was defined as sedation in which a procedure (1) was completed and the patient did not have unpleasant recall of the procedure, did not resist or require active restraint during the procedure, or did not experience a permanent complication from the sedation or (2) was not abandoned because of a sedation-level adverse event.

Outcome Measures

Four outcomes were examined for our primary objective: SAEs, significant interventions, oxygen desaturation, and vomiting. An *SAE* was defined as the occurrence of apnea, laryngospasm, hypotension, bradycardia, complete airway obstruction, clinically apparent pulmonary aspiration, permanent neurologic injury, or death. *Significant interventions* were defined as interventions performed in response to an adverse event and included positive pressure ventilation, endotracheal intubation, administration of vasoactive medications, and administration of neuromuscular blockade or chest compressions. *Oxygen desaturation* was defined as the occurrence of desaturation and the performance of 1 or more appropriate interventions to improve saturation (eg, tactile stimulation, airway repositioning, oxygen administration or increased oxygen, and positive pressure ventilation). *Vomiting* was defined as the expulsion of gastric contents through the mouth or nose during sedation induction or maintenance or during ED recovery. For our secondary objectives, *sedation medication dose* was defined as the total dose administered per kilogram of body weight. *Duration of sedation* was defined as the time from first sedation medication administration to physiologic recovery, and *ED LOS* was defined as the time from first sedation medication administration to ED discharge.

Risk Factors

Risk factors for adverse sedation outcomes were chosen a priori on the basis of clinical knowledge and literature review.[14] The primary risk factor of interest was sedation medication. Other risk factors were age, sex, body mass index (calculated as weight in kilograms divided by height in meters squared), American Society of Anesthesiologists physical status classification (ASA classification),[17] underlying health risk (health issues that may affect the efficacy of sedation or incidence of adverse events), current respiratory illness, preprocedural opioids (any opioid administered with the intent of treating pain prior to the administration of the first sedation medication), fasting status for solids (4 and 6 hours) and liquids (2 hours), procedure type, number of personnel present during the sedation, and duration of procedure. For the outcomes of vomiting and oxygen desaturation, preprocedural antiemetic administration and preoxygenation, respectively, were also examined. Risk factors were determined by patient or parental report, review of the medical record, and physical examination findings.

Statistical Analysis

The incidence of sedation-related adverse events across all 6 sites was described using frequency and percentage with 95% CI adjusted for clustering by site. Variances were estimated using the Taylor series linearization method. Bivariable associations between each risk factor and outcome were examined using the Pearson χ^2 or Fisher exact test, as appropriate. Logistic regression analysis was used to examine multivariable associations between risk factors and outcomes. To reduce the risk of bias due to small numbers of events, the logistic regression models were estimated using penalized likelihood with the Firth adjustment.[18,19] To preserve degrees of freedom, age was entered as a simple linear term after examining the assumption of linearity using empirical logit plots. The estimated odds ratios (ORs) together with 95% profile-likelihood CIs were reported; ORs for age were expressed in units of 5 years. Two-sided $P < .05$ was considered statistically significant. The goodness of fit of each model was evaluated using the Hosmer-Lemeshow test, and the discriminative ability of each model was assessed with the C statistic. To examine the sensitivity of results to variation between sites, logistic regression analyses were repeated and a random intercept for study site was added. To prevent a complete or quasi-complete separation of points in the random effects models for oxygen desaturation and vomiting, categories for some risk factors were pooled before analysis.

Subgroup analyses of patients who received ketamine alone (the largest patient subgroup) were conducted to examine the effect of total dose on outcomes by using multivariable logistic regression, as described for the primary analyses. Ketamine dose was entered as a simple linear term after examining the assumption of linearity using empirical logit plots.

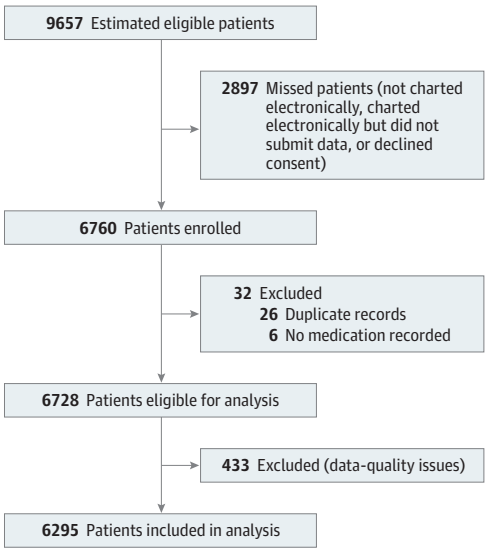
Sedation medication dose, duration of sedation, and ED LOS across categories of sedation medications were described using median and interquartile range (IQR). Statistical analyses were conducted using SAS, version 9.4 (SAS Institute Inc) and R, version 3.0.2 (R Foundation for Statistical Computing).

Results

Patient Characteristics

An estimated 9657 patients were eligible for inclusion in the study, of whom 6760 (70.0%) were enrolled and registered in the database and 6295 (65.1%) were included in the final analysis (**Figure 1**). Of the 6760 records entered in the database, 32 were removed because they were duplicates or did not indicate use of sedation medication. Baseline clinical and demographic characteristics for patients included in the study are provided in **Table 1**. Of the 6295 included patients, 4190 (66.6%) were male and the mean (SD) age was 8.0 (4.6) years. Ketamine alone was the most commonly used sedation medication (administered to 3916 patients [62.2%]), and orthopedic reduction was the most common indication for sedation (undergone by 4148 patients [65.6%]). Median doses of sedation medication by sedation group are presented in eTable 2 in the

Figure 1. Study Flowchart



Supplement. Missed patients (2897 [29.9%]) were similar to included patients in age (mean [SD], 7.6 [4.4] years vs 8.0 [4.6] years), male sex (57.2% vs 66.6%), and adverse event rate (11.2% vs 11.7%), but they differed in choice of sedation medication. Among missed patients, the prevalence of ketamine use was 7.5%, while use of the combination of propofol and fentanyl citrate was 38.1%. In contrast, included patients used ketamine in 3916 (62.2%) sedations and used the combination of propofol and fentanyl in 726 (11.5%) sedations. These differences resulted from lower enrolment rates in some sites with unique practice patterns.

Incidence of Sedation-Related Adverse Events

Overall, there were 831 adverse events in 736 patients (11.7%; 95% CI, 6.4%-16.9%). Oxygen desaturation (353 [5.6%]; 95% CI, 2.0%-9.2%) and vomiting (328 [5.2%]; 95% CI, 2.4%-8.0%) were the most common events (**Table 2**). There were no cases of complete airway obstruction, pulmonary aspiration, neurologic injury, or death. There were 69 SAEs (1.1%; 95% CI, 0.5%-1.7%) SAEs, comprising apnea (55 [0.9%]), laryngospasm (4 [0.1%]), hypotension (7 [0.1%]), and bradycardia (3 [0.1%]). Significant interventions in response to an adverse event occurred in 86 patients (1.4%; 95% CI, 0.7%-2.1%). Positive pressure ventilation was the only significant intervention performed. Overall, 95% of sedations were successful; 58 procedures (0.9%) could not be completed under sedation, and 256 patients (4%) showed active resistance to completing a procedure. There were no unplanned admissions to hospital owing to a sedation-related adverse event.

Risk Factors of Adverse Events

The observed frequencies of outcomes for each risk factor and the bivariable tests of associations are presented in eTable 3 in the Supplement. Of all the risk factors examined, body mass index and personnel present could not be included owing to incomplete documentation.

Table 1. Baseline Clinical and Demographic Characteristics of 6295 Patients Included in the Final Analysis

Characteristic	Frequency, No. (%)
Male	4190 (66.6)
Age, mean (SD), y	8.0 (4.6)
Age <2 y	946 (15.0)
ASA class I or II	6278 (99.7)
Underlying health risk[a]	201 (3.2)
Respiratory illness	516 (8.2)
Fasting duration	
NPO solid ≤6 h	2974 (48.1)
NPO solid ≤4 h	1000 (16.2)
NPO liquid ≤2 h	310 (5.01)
Preprocedural opioid use	1812 (28.8)
Preprocedural opioid + orthopedic reduction (n = 1812)	1605 (88.6)
Preprocedural antiemetic use	1951 (31.0)
Preprocedural antiemetic + ketamine hydrochloride sedation (n = 1951)	1820 (93.3)
Procedure type	
Orthopedic reduction	4148 (65.6)
Laceration repair	1028 (16.3)
Abscess I + D	322 (5.1)
Foreign-body removal	222 (3.5)
Lumbar puncture	150 (2.4)
Other[b]	425 (6.7)
Sedation medication	
Ketamine alone	3916 (62.2)
Combination of ketamine + midazolam hydrochloride	246 (3.9)
Combination of ketamine + propofol	851 (13.5)
Combination of ketamine + fentanyl citrate	219 (3.5)
Combination of propofol + fentanyl	726 (11.5)
Propofol alone	244 (3.9)
Other[c]	93 (1.5)

Abbreviations: ASA, American Society of Anesthesiologists[17]; I + D, incision and drainage; NPO, nothing by mouth.

[a] Underlying health risk includes stridor when awake, large tongue, micrognathia, preexisting neurologic impairment, history of sleep apnea and snoring, gastroesophageal reflux, chronic constipation, or vomiting.

[b] Other procedure type includes dental, paraphimosis reduction, joint aspiration, cast application, wound debridement, dressing change, inguinal hernia reduction, chest tube insertion, traction, catheterization, and rectal prolapse reduction.

[c] Other sedation medication includes pentobarbital sodium, nitrous oxide, and etomidate.

Ketamine alone had the lowest observed incidence of SAEs (17 [0.4%]) and significant interventions (37 [0.9%]). Propofol alone and the combinations of ketamine and fentanyl and of ketamine and propofol had the highest observed incidences of SAEs (9 [3.7%] for propofol alone, 7 [3.2%] for ketamine and fentanyl combined, and 18 [2.1%] for ketamine and propofol combined). The highest numbers of significant interventions occurred with the use of ketamine and fentanyl combined (9 observed incidences [4.1%]) and ketamine and propofol combined (21 [2.5%]), which also had the highest observed incidences of oxygen desaturation (31 [14.1%] for ketamine and fentanyl combined and 76 [8.9%] for ketamine and propofol combined).

Results from the multivariable logistic regression analyses of SAEs, significant interventions, oxygen desaturation, and vomiting are summarized in **Figure 2** and eTable 4 in the Supplement.

Serious Adverse Events

Sedation medication was the only risk factor significantly associated with SAEs. Compared with ketamine alone, all categories of medications were associated with significantly increased odds of an adverse event. The greatest associations were for propofol alone (OR, 5.6; 95% CI, 2.3-13.1) and for the combinations of ketamine and fentanyl (OR, 6.5; 95% CI, 2.5-15.2) and ketamine and propofol (OR, 4.4; 95% CI, 2.2-8.7).

Significant Interventions

Compared with ketamine alone, sedation with a combination of ketamine and fentanyl (OR, 4.0; 95% CI, 1.8-8.1) and of ketamine and propofol (OR, 2.2; 95% CI, 1.2-3.8) were associated with increased odds of significant intervention. Other significant risk factors were preprocedural opioid administration (OR, 2.2; 95% CI, 1.4-3.5), laceration repair (OR, 2.4; 95% CI, 1.1-4.7), and age (OR, 1.8; 95% CI, 1.3-2.5).

Oxygen Desaturation

Compared with ketamine alone, sedation achieved with a combination of ketamine and fentanyl (OR, 2.5; 95% CI, 1.5-3.8) and of ketamine and propofol (OR, 2.2; 95% CI, 1.6-3.0) were significantly associated with oxygen desaturation. Preprocedural opioids (OR, 2.1; 95% CI, 1.6-2.6), age (OR, 1.3; 95% CI, 1.1- 1.5), and laceration repair (OR, 1.6; 95% CI, 1.1- 2.3) or lumbar puncture (OR, 2.8; 95% CI, 1.4- 5.1) were also significantly associated with desaturation.

Vomiting

The only sedation medication significantly associated with more emesis than ketamine alone was the combination of ketamine and fentanyl (OR, 1.9; 95% CI, 1.2-2.8). Preprocedural opioids and laceration repair were significantly associated with an increased odds of vomiting by 50% (OR, 1.5; 95% CI, 1.1-1.9) and 70% (OR, 1.7; 95% CI, 1.2-2.4), respectively, whereas preprocedural antiemetics were significantly associated with decreased odds (OR, 0.5; 95% CI, 0.4-0.7).

The sensitivity analyses accounting for between-center variation using random effects models are presented in eTable 5 in the Supplement. Results for sedation medication were similar to those from the penalized logistic regression analyses.

Sedation Medication Dose and Adverse Events

In the subset of 3916 patients who received ketamine alone (median [IQR] dose, 1.5 [1.0-2.0] mg/kg), ketamine dose was not significantly associated with SAEs or significant interventions. However, we found a significant association of higher dose with oxygen desaturation (OR, 1.3; 95% CI, 1.1-1.6) and vomiting (OR, 1.3; 95% CI, 1.1-1.5) (eTable 6 in the Supplement).

Sedation Time Intervals

Descriptive summaries of sedation duration within categories of sedation medications are presented in eTable 7 in the Supplement. Sedation with propofol alone was associated with the shortest sedation duration (median [IQR], 51 [45-126] minutes) and ED LOS (median [IQR], 67 [43-196] minutes), whereas the combination of ketamine and fentanyl had the longest sedation duration (177 [84-145]) and ED LOS (132 [100-164] minutes).

Table 2. Adverse Events in Procedural Sedation Across All Study Sites

Adverse Event	No. (%) [95% CI][a]
Serious adverse events	69 (1.1) [0.5-1.7]
Apnea	55 (0.9) [0.3-1.4]
Laryngospasm	4 (0.1) [0.0-0.2]
Hypotension	7 (0.1) [0.0-0.2]
Bradycardia	3 (0.1) [0.0-0.1]
Complete airway obstruction	0 [NA]
Clinically apparent pulmonary aspiration	0 [NA]
Permanent neurological injury	0 [NA]
Death	0 [NA]
Oxygen desaturation	353 (5.6) [2.0-9.2]
Vomiting	328 (5.2) [2.4-8.0]
Partial airway obstruction	45 (0.7) [0.5-1.0]
Myoclonus	16 (0.3) [0.1-0.4]
Paradoxical response	13 (0.2) [0.1-0.3]
Seizure	5 (0.1) [0.0-0.2]
Muscle rigidity	2 (0.03) [0.0-0.1]

Abbreviation: NA, not applicable.

[a] All SEs were adjusted for clustering by site and estimated using the Taylor series linearization method.

Discussion

The overall incidence of adverse events in our population was 736 patients (11.7%; 95% CI, 6.4%-16.9%). Oxygen desaturation (353 [5.6%]) and vomiting (328 [5.2%]) were the most common events. The low rate of SAEs (1.1%; 95% CI, 0.5%-1.7%) reported supports the safety of procedural sedation in the hands of emergency department physicians.

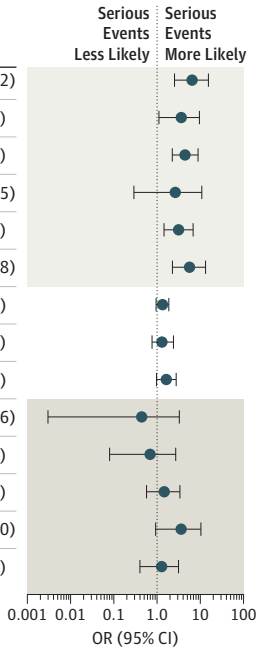
The incidence of SAEs and significant interventions was lowest among patients sedated with ketamine alone and was highest among patients sedated with combination drugs ketamine and propofol as well as ketamine and fentanyl. After adjusting for other risk factors, these combination medications were associated, respectively, with a 4-fold and 6.5-fold increase in the odds of SAEs, a 2-fold and 4-fold increase in significant intervention, and a 2-fold increase in oxygen desaturation. Although propofol alone and the combination of propofol and fentanyl were associated with a 3-fold and 5-fold increase in the odds of an SAE, significant interventions in response to these events were not increased. This finding is likely because propofol-associated events are transient and are commonly resolved with only minor intervention.

Our findings about the combination of ketamine and propofol are important because "ketofol" use in ED sedation has increased dramatically over the past decade.[20,21] Some clinicians believe the sedation experience is improved because combination use offsets each individual agent's limitations. Small case series and randomized trials have not shown a difference in adverse event rates between ketofol and ketamine or propofol

Figure 2. Multivariable Regression Models: Risk Factors Associated With Sedation Outcomes

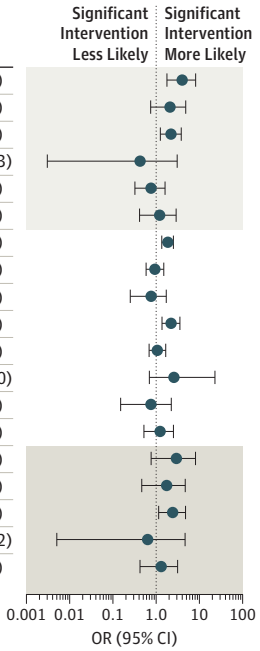
A Risk factors for serious adverse events

Factor	OR (95% CI)
Ketamine + fentanyl[a]	6.48 (2.52-15.22)
Ketamine + midazolam[a]	3.60 (1.10-9.45)
Ketamine + propofol[a]	4.42 (2.25-8.74)
Other medication[a]	2.62 (0.29-10.75)
Propofol + fentanyl[a]	3.15 (1.45-6.74)
Propofol only[a]	5.59 (2.27-13.08)
Age in 5 y	1.34 (0.95-1.84)
Male	1.30 (0.76-2.37)
Preprocedural opioid	1.63 (1.97-2.73)
Foreign-body removal[b]	0.44 (<0.01-3.26)
Abscess incision + drainage[b]	0.69 (0.08-2.68)
Laceration repair[b]	1.46 (0.57-3.34)
Lumbar puncture[b]	3.58 (0.92-10.30)
Other procedures[b]	1.27 (0.40-3.12)



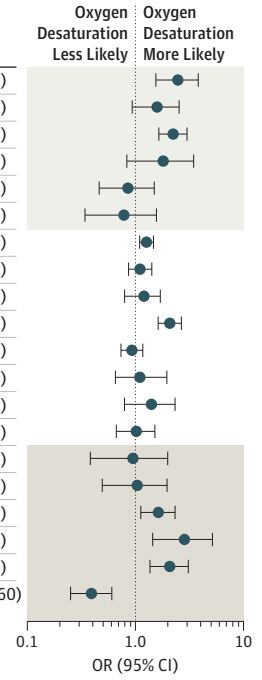
B Risk factors for significant intervention

Factor	OR (95% CI)
Ketamine + fentanyl[a]	3.97 (1.77-8.14)
Ketamine + midazolam[a]	2.08 (0.74-4.79)
Ketamine + propofol[a]	2.18 (1.24-3.70)
Other medication[a]	0.42 (<0.01-3.03)
Propofol + fentanyl[a]	0.76 (0.32-1.59)
Propofol only[a]	1.19 (0.41-2.87)
Age in 5 y	1.84 (1.34-2.49)
Male	0.92 (0.58-1.49)
ASA classification	0.79 (0.25-1.70)
Preprocedural opioid	2.18 (1.36-3.52)
Fasting compliant for solids	1.05 (0.68-1.65)
Fasting compliant for liquids	2.56 (0.69-22.80)
Underlying health risk	0.75 (0.15-2.22)
Current respiratory illness	1.22 (0.52-2.48)
Foreign-body removal[b]	2.89 (0.76-8.05)
Incision and drainage abscess[b]	1.72 (0.46-4.67)
Laceration repair[b]	2.39 (1.13-4.75)
Lumbar puncture[b]	0.63 (<0.01-4.62)
Other procedures[b]	1.30 (0.42-3.12)



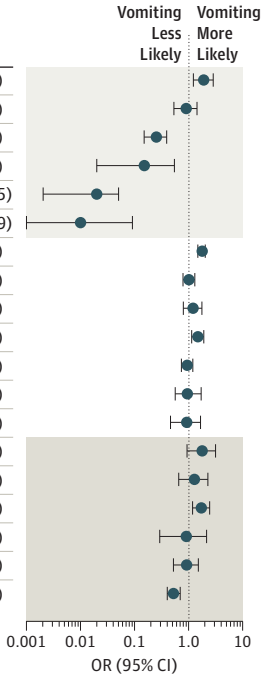
C Risk factors for oxygen desaturation

Factor	OR (95% CI)
Ketamine + fentanyl[a]	2.46 (1.54-3.80)
Ketamine + midazolam[a]	1.58 (0.93-2.52)
Ketamine + propofol[a]	2.22 (1.64-2.99)
Other medication[a]	1.79 (0.83-3.45)
Propofol + fentanyl[a]	0.85 (0.46-1.49)
Propofol	0.78 (0.34-1.56)
Age in 5 y	1.26 (1.09-1.46)
Male	1.10 (0.86-1.41)
ASA classification	1.19 (0.79-1.69)
Preprocedural opioid	2.07 (1.62-2.65)
Fasting compliant for solids	0.92 (0.73-1.16)
Fasting compliant for liquids	1.09 (0.65-1.95)
Underlying health risk	1.40 (0.79-2.32)
Current respiratory illness	1.01 (0.66-1.50)
Foreign-body removal[b]	0.94 (0.38-1.97)
Incision and drainage abscess[b]	1.03 (0.49-1.94)
Laceration repair[b]	1.61 (1.11-2.30)
Lumbar puncture[b]	2.83 (1.44-5.13)
Other procedures[b]	2.06 (1.35-3.07)
Preoxygenation	0.39 (0.25 to 0.60)



D Risk factors for vomiting

Factor	OR (95% CI)
Ketamine + fentanyl[a]	1.87 (1.21-2.82)
Ketamine + midazolam[a]	0.89 (0.53-1.42)
Ketamine + propofol[a]	0.25 (0.15-0.39)
Other medication[a]	0.15 (0.02-0.53)
Propofol + fentanyl[a]	0.02 (0.002-0.05)
Propofol	0.01 (0.001-0.09)
Age in 5 y	1.74 (1.49-2.03)
Male	1.00 (0.78-1.29)
ASA classification	1.20 (0.79-1.74)
Preprocedural opioid	1.47 (1.13-1.90)
Fasting compliant for solids	0.93 (0.73-1.18)
Fasting compliant for liquids	0.94 (0.56-1.69)
Underlying health risk	0.91 (0.46-1.65)
Foreign-body removal[b]	1.77 (0.93-3.13)
Incision and drainage abscess[b]	1.27 (0.65-2.25)
Laceration repair[b]	1.70 (1.18-2.42)
Lumbar puncture[b]	0.90 (0.29-2.13)
Other procedures[b]	0.91 (0.52-1.50)
Preprocedure antiemetics	0.52 (0.40-0.69)



Ketamine was given as ketamine hydrochloride; fentanyl, as fentanyl citrate; and midazolam, as midazolam hydrochloride. ASA indicates American Society of Anesthesiologists; OR, odds ratio.

[a] Ketamine only (lighter shaded sections).

[b] Orthopedic reduction (darker shaded sections).

alone,[22-25] but many experts have not endorsed the regular use of ketofol because no objective benefit has been demonstrated.[20] Results from our study support this expert opinion.

Higher doses of ketamine were not associated with increased odds of SAEs or significant interventions but were associated with increased odds of oxygen desaturation and vom-

iting. These findings are in opposition to the common belief that "ketamine does not exhibit any dose-related adverse events across the range of clinically administered doses," as reported in the most recent ketamine practice guideline.[26(p454)]

We found that preprocedural antiemetics were associated with a 50% reduction in the odds of vomiting. However, published evidence has shown that their use in children younger than 5 years may not be as advantageous because their baseline risk is much lower.[27,28]

Preprocedural opioid administration was strongly associated with increased odds of all outcomes except SAEs, regardless of the sedation medication used. Although we do not recommend limiting opioid use to treat preprocedural pain, we believe that awareness of this risk factor will help clinicians prepare for sedation and anticipate potential adverse events.

Undergoing a laceration repair was the only procedure associated with increased odds of all outcomes except SAEs. The cause and significance of this association remains to be determined.

Many ED procedural sedation studies examine adverse events, but most have not been able to comment on SAEs because of their infrequent occurrence. To our knowledge, only 1 ED study has a sample size that is larger than ours: Green et al[6,27] aggregated and reanalyzed data from 32 ED studies of ketamine sedation, creating a cohort of 8282 patients. Green and colleagues' 2011 study is limited by clinical and methodologic heterogeneity,[29] but we found a similar rate of SAEs and low rates of adverse events overall.

The Pediatric Sedation Research Consortium is a large collaborative that gathers data on pediatric sedation outside the operating room.[8,30,31] However, that cohort contains few ED patients, many patients have serious comorbidities (17% of whom are categorized under American Society of Anesthesiologists class III or higher), and most patients undergo long, elective sedations (60% of which are diagnostic imaging).[18] These differences prevent the generalizability of the consortium's results to the ED setting, where generally healthy children are sedated for short, emergent, and mostly painful procedures.

Strengths and Limitations

Our study has several strengths. It represents the largest, most robust prospective ED procedural sedation cohort to date, using standardized outcome definitions and a novel documentation process that helped ensure data integrity. The inclusion of children from 6 EDs who were sedated with 6 different medications or combinations of medications for a range of painful procedures represents the breadth of ED sedation and substantially enhances the generalizability of our results. We have been able to both support and refute expert opinion where there was previously limited clinical evidence to guide practice. To our knowledge, this study is the first prospective ED study to comprehensively examine risk factors for sedation-related SAEs.

Our study also has several limitations. First, because it was an observational study, direct causal conclusions should not be drawn from our results. Furthermore, our results could be confounded by indication. We attempted to adjust for all known risk factors in our multivariable models, but there could be other unmeasured factors for which we were unable to account. Second, we did not conduct daily surveillance for missed patients. There were no cases of sedation-related pulmonary aspiration, neurologic injury, or death during the study period at any of our study sites; however, it is possible that other SAEs were missed during nonsurveillance weeks. Third, all of the study sites were tertiary care academic children's hospitals, which may limit the generalizability of our results to practice in general hospitals. Fourth, practice variation in response to events is a potential limitation of the Quebec Guidelines,[15] from which our adverse event definitions were derived. Finally, despite our large sample size, some events (eg, pulmonary aspiration) did not occur, allowing us to conclude that the risk of these events was no more than 3.1 in 10 000 sedations.[32]

Conclusions

The large, multicenter cohort in this study shows that ED procedural sedation for children in this setting is safe, with a low overall incidence of SAEs and interventions. Sedation with ketamine alone was associated with the best outcomes, with significantly fewer SAEs and interventions than ketamine combined with either propofol or fentanyl.

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