

Predictors of Airway and Respiratory Adverse Events With Ketamine Sedation in the Emergency Department: An Individual-Patient Data Meta-analysis of 8,282 Children

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Study objective: Although ketamine is one of the most commonly used sedatives to facilitate painful procedures for children in the emergency department (ED), existing studies have not been large enough to identify clinical factors that are predictive of uncommon airway and respiratory adverse events.

Methods: We pooled individual-patient data from 32 ED studies and performed multiple logistic regressions to determine which clinical variables would predict airway and respiratory adverse events.

Results: In 8,282 pediatric ketamine sedations, the overall incidence of airway and respiratory adverse events was 3.9%, with the following significant independent predictors: younger than 2 years (odds ratio [OR] 2.00; 95% confidence interval [CI] 1.47 to 2.72), aged 13 years or older (OR 2.72; 95% CI 1.97 to 3.75), high intravenous dosing (initial dose ≥ 2.5 mg/kg or total dose ≥ 5.0 mg/kg; OR 2.18; 95% CI 1.59 to 2.99), coadministered anticholinergic (OR 1.82; 95% CI 1.36 to 2.42), and coadministered benzodiazepine (OR 1.39; 95% CI 1.08 to 1.78). Variables without independent association included oropharyngeal procedures, underlying physical illness (American Society of Anesthesiologists class ≥ 3), and the choice of intravenous versus intramuscular route.

Conclusion: Risk factors that predict ketamine-associated airway and respiratory adverse events are high intravenous doses, administration to children younger than 2 years or aged 13 years or older, and the use of coadministered anticholinergics or benzodiazepines. [Ann Emerg Med. 2009;54:158-168.]

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0196-0644/\$-see front matter

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doi:10.1016/j.annemergmed.2008.12.011

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Editor's Capsule Summary

What is already known on this topic

Ketamine is commonly used for pediatric sedation. Although its complications are well known, their frequency and the factors that predispose patients to complications are not.

What question this study addressed

This 8,282 individual-patient (32 reports) meta-analysis summarizes complications of ketamine use and their association with patient demographics and characteristics of the sedation procedure.

What this study adds to our knowledge

The study suggests that respiratory and airway events are more common in teenagers and infants younger than 2 years, those receiving higher intravenous doses, and those receiving concurrent benzodiazepines or anticholinergics.

How this might change clinical practice

Physicians using ketamine for sedation may want to rethink their intravenous dosing strategy and their use of concurrent benzodiazepines or anticholinergics.

SEE EDITORIAL, P. 169.

INTRODUCTION

Background

The efficacy and safety of ketamine to facilitate painful procedures for children in the emergency department (ED) have been documented in 57 published series totaling nearly 10,000 patients.¹⁻⁵⁷ This dissociative agent is the most commonly used sedative in the United States for this indication.⁵⁸⁻⁶⁴ Airway and respiratory adverse events occur in 1.4% to 6.6% of ketamine sedations,^{2,19} including laryngospasm in approximately 0.4%.² Given the rarity of these airway events, previous investigations have, because of their small size, been unable to determine whether they are related to ketamine dose, administration route, or coadministered drugs (eg, anticholinergics, benzodiazepines) or whether they are related to patient variables such as age or underlying illness.⁵⁵

Importance

If specific differences in ketamine technique or patient variables are predictive of airway adverse events, then emergency physicians may elect to modify their administration technique or patient selection to minimize such adverse events.

Goals of This Investigation

We pooled original data from all available series of ED ketamine sedation in children to identify clinical predictors of

airway and respiratory adverse events. Secondary goals were to perform similar analyses for the subsets of children with laryngospasm and apnea.

MATERIALS AND METHODS

Study Design

We performed a meta-analysis in accordance with Quality of Reporting of Meta-analyses (QUOROM) guidelines⁶⁵ of all available original data from existing ketamine case series. All included trials had local ethics committee approval.

We searched the PubMed electronic database for articles of any language published between 1966 and May 2008, using the key words "ketamine" and "emergency." The reference lists of identified articles were examined for additional studies missed by the MEDLINE search. Finally, we contacted authors of identified ketamine series to determine whether they were aware of other reports missing from our listing.

We included full-length reports that contained a discrete series of parenteral ketamine administrations in children (defined as age ≤ 21 years) for ED procedural sedation. We excluded abstracts, case reports, case-control studies, series with fewer than 20 subjects, and series in which the individual patient data did not include doses and adverse effects or had been discarded by their study authors. We also excluded reports in which propofol was coadministered because the latter drug is a more potent respiratory depressant^{63,64} than the more commonly coadministered midazolam and might confound the analysis of airway adverse events.

Data Collection and Processing

We contacted study authors of qualifying reports and asked them to submit their original data in electronic format to a central repository, with their submission stripped of all patient identifiers and restricted to the variables selected for the meta-analysis. Authors were queried about any missing data points and were asked to recode their variables as needed to comply with our study definitions.

Outcome Measures

The primary outcome for this study was the overall occurrence of airway and respiratory adverse events, with secondary outcomes the specific occurrence of laryngospasm and apnea. We defined airway/respiratory adverse events as an occurrence of any of the following: upper airway obstruction (stridor, hypoventilation, or oxygen desaturation that resolved with repositioning of the airway), apnea (cessation of spontaneous respirations considered to be significant by observers and recorded as such), abnormal oxygen saturation (decrease in oxygen saturation to $\leq 90\%$ at any point), or laryngospasm (stridor or other evidence of airway obstruction that did not improve with airway alignment maneuvers).

Candidate predictor variables were selected according to previous literature and biological plausibility of association with airway adverse events.

The ketamine technique variables chosen were route (coded as intravenous versus intramuscular), initial dose (in mg/kg), total dose (in mg/kg), the presence or absence of coadministered anticholinergics (eg, atropine, glycopyrrolate), and the presence or absence of coadministered benzodiazepines (eg, midazolam, diazepam).

The patient variables chosen were age, American Society of Anesthesiologists (ASA) physical status,^{63,64} and oropharyngeal procedural indication (coded as present versus absent).

Primary Data Analysis

We examined the frequency distributions for the continuous variables, and if their distributions were found to be bimodal the variables were instead dichotomized at logical thresholds. We performed separate multiple logistic regression analyses for each of the 3 outcomes (ie, airway and respiratory adverse events, laryngospasm, apnea). For each multivariate analysis, we restricted the number of predictor variables to approximately 10% of the number of airway and respiratory event outcome observations to minimize the risk of overfitting, in accordance with standard recommendations.⁶⁶⁻⁶⁹ We used this a priori approach according to our judgment of the highest biological plausibility of association. We calculated the likelihood ratios and area under the receiver operating characteristic curve for each model and performed goodness-of-fit analyses with the Hosmer-Lemeshow test. All such analyses were performed with Stata 9 software (StataCorp, College Station, TX).

Because of concerns about potential underreporting of adverse events in retrospective research, we also performed mirrored analyses by using just the subset with prospectively obtained data. Our a priori intent was that if the prospective subset analyses disagreed from their overall counterparts, then the prospective subsets would be deemed the more reliable, given their stronger methodology. If the prospective subset analyses agreed with their overall counterparts, then the overall analysis would be considered reliable.

RESULTS

The results of the literature search and article processing are shown in Figure 1. Data from 32 reports were ultimately included (Table 1), comprising 8,353 aggregate ketamine sedations. We then excluded 71 individual sedations (0.85%) from the overall database for the following reasons: missing total ketamine dose (n=47), missing documentation of benzodiazepine use (n=12), use for intubation rather than procedural sedation (n=10), missing age (n=1), and age greater than 21 years (n=1). There were no airway or respiratory adverse events in this excluded group.

Characteristics of Study Subjects

Characteristics of the 8,282 remaining sedations are shown in Table 2. The overall rate of airway or respiratory adverse events was 3.9%, including 0.3% with laryngospasm and 0.8% with apnea. No children were intubated or received paralytics in

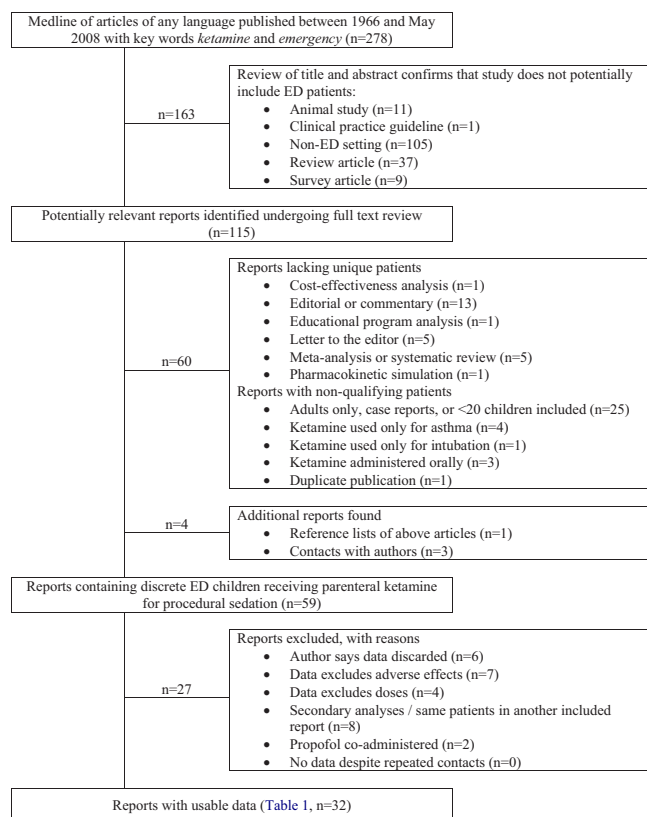


Figure 1. Meta-analysis trial flow profile.

the management of these adverse events, and the 95% confidence interval of this 0% incidence ranges up to 0.04%.

When we examined the frequency distributions for the outcomes stratified by age, we visually observed bimodal distributions (Figure 2). Accordingly, rather than using age as a continuous variable, we divided it into 3 groups according to the figure and compared children younger than 2 years and aged 13 years or older to the reference group of those in between.

Initial ketamine dose was not collected in 5 studies^{10-12,20,32} comprising 1,536 sedations (18.5%). As with age, the frequency distributions for outcomes stratified by initial and total dose (Figures 3 to 6) were also not log-linear and therefore not appropriate for retention as continuous variables. They also differed between intramuscular and intravenous routes, with an apparent threshold at the lower end of intramuscular dosing and at the higher end of intravenous dosing. Accordingly, we divided dose into 3 groups and compared those with low intramuscular dosing (total dose <3.0 mg/kg) and those with high intravenous dosing (initial dose ≥ 2.5 mg/kg or total dose ≥ 5.0 mg/kg) to the reference group of the remainder.

The type of procedure was missing in 43 (0.5%) sedations, and given that oropharyngeal procedures were unusual in the overall data set (3.4%), we coded these missing entries as nonoropharyngeal. Coadministered anticholinergic use was not recorded in 322 sedations (3.9%) in one study¹²; however, because the practice pattern at this institution during this period

Table 1. Included ED ketamine reports (n=32).

Reference	Study	Format	Sedations	Airway Adverse Events, No. (%)	Laryngospasm, No. (%)	Apnea, No. (%)
1	1997 Dachs	Prospective	30	0 (0)	0 (0)	0 (0)
2	1998 Green	Mixed	1,022	14 (1.4)	4 (0.4)	2 (0.2)
3	1998 Green	Retrospective	156	2 (1.3)	0 (0)	2 (1.3)
4	1999 Pena	Prospective	220	4 (1.8)	1 (0.5)	0 (0)
5	2000 Holloway	Retrospective	81	1 (1.2)	1 (1.2)	0 (0)
6	2000 Sherwin	Prospective	104	0 (0)	0 (0)	0 (0)
7	2001 Acworth	Prospective	26	1 (3.8)	0 (3.8)	0 (0)
8	2001 Gloor	Prospective	200	53 (26.5)	3 (1.5)	27 (13.5)
9	2001 Priestley	Prospective	28	0 (0)	0 (0)	0 (0)
10	2002 Hostetler	Prospective	301	11 (3.7)	0 (0)	0 (0)
11	2002 Hostetler	Retrospective	57	6 (10.5)	1 (1.8)	2 (3.5)
12	2003 Agrawal	Prospective	473	19 (4.0)	2 (0.4)	7 (1.5)
13	2003 Godambe	Prospective	54	4 (7.4)	0 (0)	0 (0)
14	2003 Kim	Prospective	20	1 (5.0)	0 (0)	0 (0)
15	2003 Pitetti	Prospective	351	26 (7.4)	2 (0.6)	1 (0.3)
16	2004 Ellis	Prospective	89	0 (0)	0 (0)	0 (0)
17	2004 Imak	Prospective	26	2 (7.7)	1 (3.8)	1 (3.8)
18	2004 McGlone	Prospective	507	4 (0.8)	0 (0)	0 (0)
19	2004 Roback	Prospective	1,519	95 (6.3)	2 (0.1)	13 (0.9)
20	2004 Treston	Prospective	272	0 (0)	0 (0)	0 (0)
21	2005 Green	Prospective	26	0 (0)	0 (0)	0 (0)
22	2005 Oktay	Prospective	141	2 (1.4)	1 (0.7)	0 (0)
23	2006 Heinz	Prospective	82	1 (1.2)	0 (1.2)	0 (0)
24	2006 Kriwanek	Prospective	21	0 (0)	0 (0)	0 (0)
25	2006 Losek	Retrospective	143	7 (4.9)	0 (0)	1 (0.7)
26	2006 Luhmann	Prospective	55	0 (0)	0 (0)	0 (0)
27	2006 Roback	Prospective	208	14 (6.7)	1 (0.5)	2 (1.0)
28	2006 Wissler	Retrospective	453	2 (0.4)	0 (0)	2 (0.4)
29	2007 Bleiberg	Retrospective	72	1 (1.3)	0 (0)	3 (4.2)
30	2007 Herd	Prospective	60	0 (0)	0 (0)	0 (0)
31	2008 Brown	Prospective	1,085	42 (3.9)	3 (0.3)	0 (0)
32	2008 McKee	Retrospective	471	7 (1.5)	0 (0)	0 (0)
	Total		8,353	319	22	63
	Percentage			3.82	0.26	0.75

was to administer anticholinergics, we coded these as positive. Given that multiple studies coded ASA physical status as either class 1 or 2, we dichotomized this variable as ASA 1 or 2 versus ASA greater than or equal to 3. ASA status was missing in 10 cases from a single study,²⁵ and because this author believed that these children were almost certainly ASA 1 or 2, we coded them in this fashion.

Unadjusted comparisons of predictor variables by outcome are shown in Appendices E1 to E3 (available online at <http://www.annemergmed.com>).

The final predictor variable list thus included no continuous variables, 2 three-part categorical variables (age and dose), and 5 binary variables (route, oropharyngeal procedure, ASA, anticholinergic, benzodiazepine).

The number of total outcomes was sufficient to include all predictor variables for total airway and respiratory adverse events and for apnea, but not for laryngospasm. Given only 22 occurrences of laryngospasm, before data analysis we selected the 3 variables that we judged to have the highest biological plausibility of association: age, dose, and oropharyngeal procedure.

The multiple logistic regression analyses are shown in Tables 3 to 5 for the total sample and for the prospective subset, demonstrating multiple significant independent predictors for each outcome.

Given the unexpected association of anticholinergics with airway and respiratory adverse events and a known potentially confounding influence of age on this factor,³¹ post hoc we repeated our analyses, adjusting for age as a continuous rather than categorical variable, but again confirmed this same outcome (data not shown).

Given the unexpected higher rate of airway and respiratory adverse events in children aged 13 years or older, post hoc we contrasted dosing by the presence or absence of airway and respiratory adverse events in this subset and overall dosing by age strata. We found similar dosing between groups (Appendix E4, available online at <http://www.annemergmed.com>) and that clinicians used lower doses on a milligram per kilogram basis with increasing age, particularly for the intravenous route (Appendix E5; available online at <http://www.annemergmed.com>).

Table 2. Descriptive characteristics of aggregate data set (n=8,282).*

Characteristics	Summary Results
Age, y	Median 5.6, IQR 3.0, 9.1 Range 0.1–19.3
Weight, kg	Median 20.3 (IQR 15.0, 32.0) Range 3.0–129.3
Initial dose (mg/kg)	
Intramuscular	Median 3.9, IQR 2.5, 4.0 Range 0.3–9.1
Intravenous	Median 1.1, IQR 1.0, 1.9 Range 0.1–9.4
Total dose, mg/kg	
Intramuscular	Median 4.0, IQR 2.9, 4.1 Range 0.4–12.0
Intravenous	Median 1.5, IQR 1.0, 2.6 Range 0.1–23.8
Procedure	
Orthopedic procedure	4,050
Wound repair excluding the oropharynx	3,072
Oropharyngeal procedure	268
Imaging	52
Other	797
ASA physical status	
1 Or 2 (not differentiated)	1,279
1	6,372
2	529
3	83
4	8
5	1
Route	
Intramuscular	2,604
Intravenous	5,678
Coadministered drugs	
Anticholinergic	5,358 (65%)
Benzodiazepine	2,740 (33%)
Airway/respiratory adverse events	
Laryngospasm	22 (0.3%)
Apnea	63 (0.8%)
Other	234 (2.8%)

*Data were missing as follows: weight 128, procedure 43, ASA 10, initial dose 1,536, and anticholinergic 322.
IQR, Interquartile range; ASA, American Society of Anesthesiologists.

LIMITATIONS

The principal limitation of this report is the heterogeneity of the collated studies and the observational nature of the data. Although the studies are similar in that they include children receiving ketamine for ED procedures, there is substantial variation in procedural indications, ages, doses, and other clinical variables, as might be expected from 32 studies coming from multiple countries. As shown in Table 1, there were differences in the rates of outcome measures between studies; these may have resulted from heterogeneity in practice style or adverse event surveillance or may be due to chance alone. It is possible that 1 or 2 larger studies with an unusual experience might have biased the overall analysis. Similarly, individual clinician practice variation in children judged at higher or lower risk of airway and respiratory adverse events may have affected the observed associations. Unfortunately, the

direction and magnitude of these effects, if present, cannot be ascertained. Alternatively, this same diversity could be argued as a major strength of the analysis because our findings are likely to have substantial external validity, given the wide spectrum of collective input.

A second limitation is that our multivariate modeling did not fit the data as strongly for overall airway and respiratory adverse events as it did for the subsets with laryngospasm and apnea. Accordingly, our findings for the overall group are likely less reliable than for the 2 subsets. We believe that this reflects the multiple types of adverse events studied (eg, partial airway obstruction, respiratory depression, laryngospasm, apnea) that are clinically distinct and influenced by differing factors. This suggests that future research should target specific individual adverse events rather than combining them into a heterogeneous global category.

A third limitation is that we were unable to study several important clinical variables because of their inconsistent recording in the collated studies. The use of supplemental oxygen might be expected to affect the incidence of hypoxemia. The presence of underlying upper respiratory infection, wheezing, or excessive salivation would be expected to increase the risk of laryngospasm.⁷⁰ Coadministered opioids may increase the risk of apnea. Differential dosing of benzodiazepines or anticholinergics might result in different effects. Specific underlying medical conditions (eg, sleep apnea, snoring) may have influenced the outcomes. Length of procedure may have influenced the association between doses and adverse events. Unfortunately, our data cannot shed light on these factors.

A fourth limitation relates to the weaknesses inherent in multiple logistic regression modeling. Some variables required dichotomization because they did not meet the distributional requisites of the technique, and it is possible that our choice of dichotomization thresholds affected the results in a direction that cannot be predicted. Further, there may have been nonindependence of the variables or interaction among variables that was not accounted for by the models.

A final limitation is that the a priori definitions of adverse events were not uniform throughout the studies. Although we asked authors to recode their data as appropriate to conform to our meta-analysis definitions, there may be some under- or overreporting of adverse events according to these differences.

DISCUSSION

In this original-data meta-analysis of 8,282 sedations collated from 32 previously published series, we report the largest ED ketamine sample to date. In contrast to a previous study of 1,021 children that failed to identify any significant predictors of ketamine-associated airway and respiratory adverse events,⁵⁵ our much larger study identified multiple independent predictors of such events. Clinicians can use these findings to modify their patient selection, dosing, and use of coadministered medications. Furthermore, these results provide

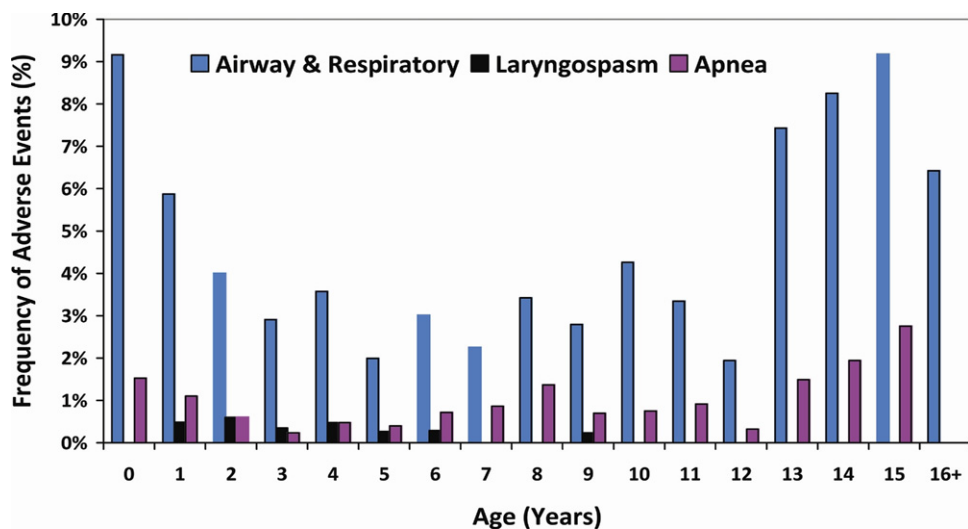


Figure 2. Frequency distribution of adverse events by age (n=8,282).

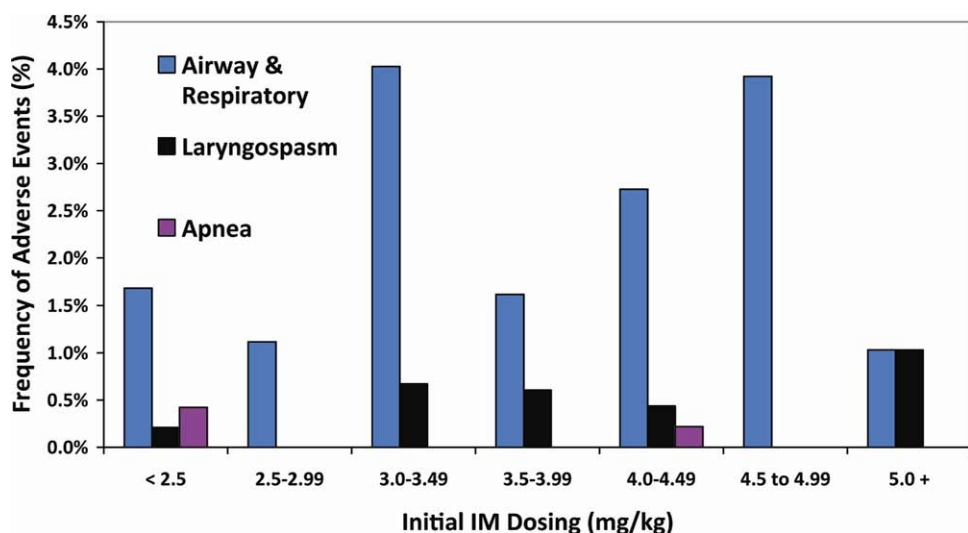


Figure 3. Frequency distribution of adverse events by initial intramuscular dosing (n=2,453).

insight into the possible underlying pathophysiology of ketamine sedation adverse events.

Our data confirm the established thinking that overall airway and respiratory adverse events are more common in the youngest children⁶⁰ because we observed approximately twice the rate of such events in those younger than 2 years. However, this age threshold was not a predictor for the subsets of children with laryngospasm or apnea, and thus this overall observed effect would appear to principally result from other airway adverse events such as partial airway obstruction. This is not unexpected, given the anatomic differences in infants relative to older children that predispose them to airway malalignment.

An unexpected finding in this analysis was that age greater than or equal to 13 years predicted more apnea, less laryngospasm, and almost 3 times the rate of overall airway and respiratory adverse events. Adolescence has not been previously

suggested as such a risk factor, and an underlying explanation for this finding is not apparent. One possibility that we considered was that clinicians might continue to use milligram per kilogram dosing in this age group when instead a fixed adult-style dose may be more appropriate; however, doses were no higher in adolescents with airway and respiratory adverse events (Appendix E4, available online at <http://www.annemergmed.com>), and clinicians were already using lower milligram per kilogram dosing in this age range, particularly for the intravenous route (Appendix E5, available online at <http://www.annemergmed.com>).

We found that high intravenous doses of ketamine (initial dose ≥ 2.5 mg/kg or total dose ≥ 5.0 mg/kg) increased by several-fold the risk of airway and respiratory adverse events, primarily through an increase in apnea. Lower loading doses (eg, 1.5 mg/kg intravenous⁶⁰) produce satisfactory dissociation and procedural conditions, and thus there is no clinical advantage to using such

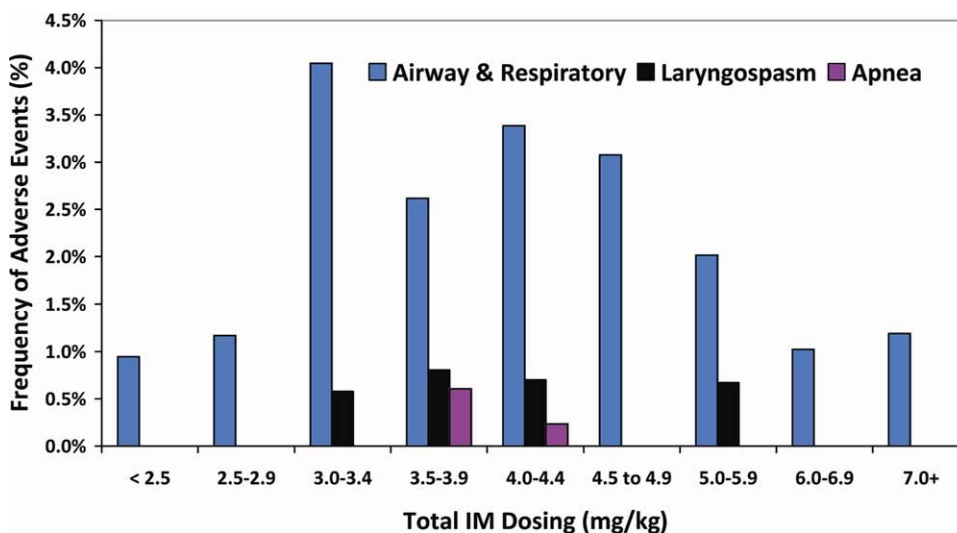


Figure 4. Frequency distribution of adverse events by total intramuscular dosing (n=2,604).

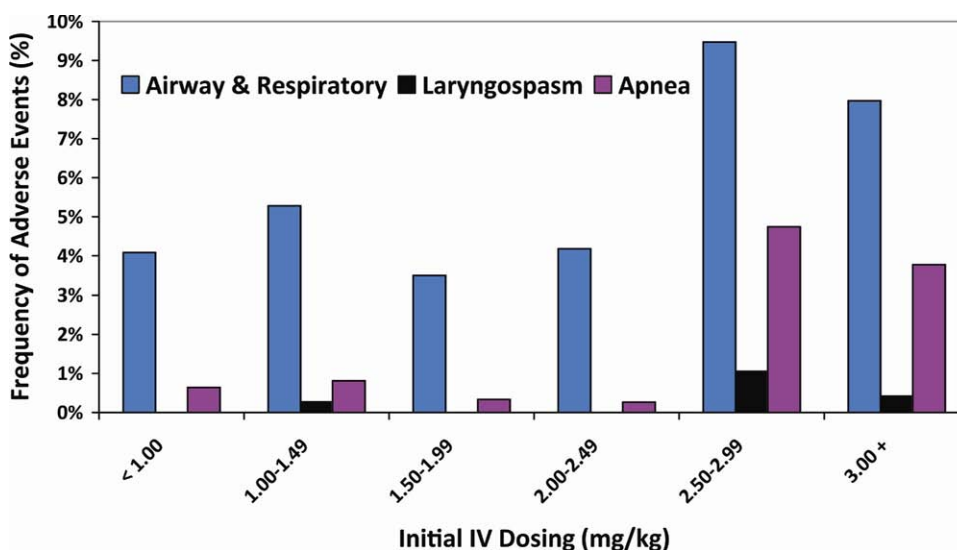


Figure 5. Frequency distribution of adverse events by initial intravenous dosing (n=4,293).

large initial doses. The higher rate of adverse events associated with high total ketamine doses may reflect the enhanced cumulative risk from multiple, repeated doses of this drug.

We found that low intramuscular doses of ketamine (<3.0 mg/kg) exhibited significantly fewer overall airway and respiratory adverse events, a finding at odds with a previous study that observed no such difference.⁵⁴ There were no occurrences of either laryngospasm or apnea in the 682 children receiving lower dosing. This strongly supports the contention of McGlone et al¹⁸ that low intramuscular dosing is likely to be the safest overall format for ED ketamine. Such dosing is typically below the threshold of clinical dissociation⁶⁰ and thus is suitable only for minor procedures requiring only analgesia and anxiolysis or minor procedures using local anesthesia. This apparent advantage of subdissociative dosing appears to apply only to the intramuscular route because we observed no

apparent decrease in airway adverse events with roughly equipotent intravenous ketamine (<1 mg/kg) (Figures 5 and 6).

Other than the 2 dosing subgroups identified above (high intravenous dose, low intramuscular dose), we found no other apparent association of ketamine dose to airway and respiratory adverse events (Figures 3 to 6). This is in marked distinction to other parenteral procedural sedation agents (eg, opioids, sedative/hypnotics) in which proportional dose-related increases in such events are evident over the full spectrum of doses administered.^{63,64} This suggests that, as long as excessively high intravenous doses are avoided, emergency physicians may use doses such as 2 mg/kg intravenously rather than 1 mg/kg intravenously, or 5 mg/kg intramuscularly rather than 3 mg/kg intramuscularly, without increased risk of adverse events.

Oropharyngeal procedures are thought to increase the risk of ketamine-associated airway adverse events.^{60,71} Laryngospasm has

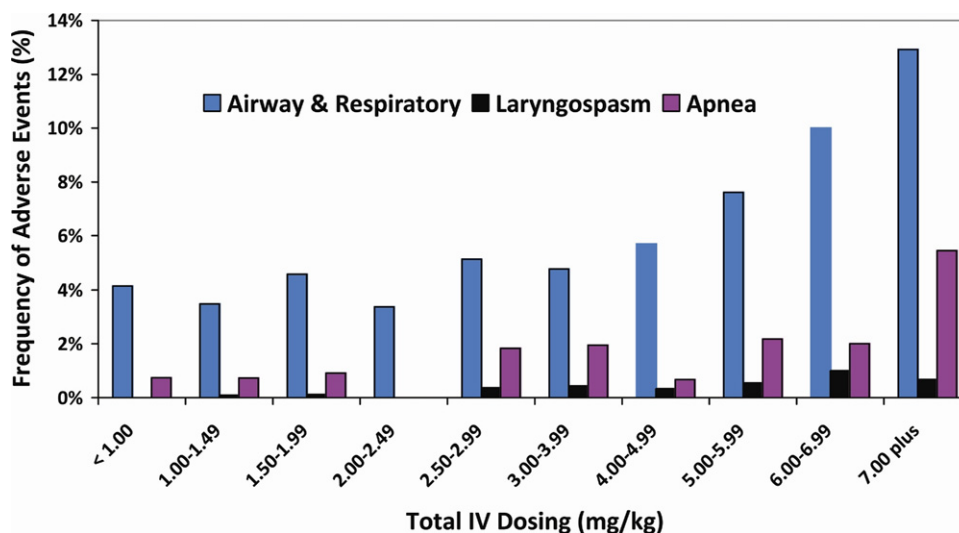


Figure 6. Frequency distribution of adverse events by total intravenous dosing (n=5,678).

Table 3. Multiple logistic regression model of airway/respiratory adverse events.

Variable	Odds Ratio (95% CI)	
	Total Sample (n=8,282)	Prospective Subset (n=6,289)
Age <2 y*	2.00 (1.47–2.72)	1.86 (1.35–2.57)
Age ≥13 y*	2.72 (1.97–3.75)	2.82 (2.01–3.97)
Low intramuscular dose [†]	0.35 (0.16–0.76)	0.25 (0.11–0.60)
High intravenous dose [†]	2.18 (1.59–2.99)	3.93 (2.82–5.47)
Oropharyngeal procedure	2.01 (1.29–3.12)	1.30 (0.77–2.18)
ASA ≥3	1.48 (0.58–3.72)	2.28 (0.86–6.04)
Intravenous route (relative to intramuscular)	1.38 (0.99–1.90)	1.12 (0.79–1.59)
Anticholinergic	1.82 (1.36–2.42)	1.51 (1.11–2.06)
Benzodiazepine	1.39 (1.08–1.78)	1.60 (1.24–2.08)

CI, Confidence interval.

The area under the model receiver operator curve is 0.687. The model demonstrated unsatisfactory goodness of fit, with the Hosmer-Lemeshow $P=.0015$. Examination of regression diagnostics revealed 1 gross outlier; when this patient was deleted and the analysis repeated, the Hosmer-Lemeshow was satisfactory ($P=.0553$), with essentially identical odds ratios and P values. This same process with a single outlier was repeated for the prospective subset.

*Reference group aged 2 to <13 years.

[†]Reference group children without low intramuscular or high intravenous dosing.

been observed in 8.2% of children when ketamine is used for endoscopy.⁷¹ We observed conflicting results for this factor. Despite significant unadjusted associations and prediction in the overall multivariate models, this factor was not a significant predictor in the more reliable prospective subset of the data (Tables 3 to 5). Typical ED oropharyngeal procedures involve substantially less throat stimulation than endoscopy, and this difference likely explains the lack of additional risk evident from our data.

With all nondissociative agents, the risk of adverse events is thought to be proportional to the degree of underlying physical illness, as is typically quantified by using the ASA physical status classification.^{63,64} Such an association has not been similarly observed with ketamine,^{55,71,72} and the cardiopulmonary

Table 4. Multiple logistic regression model of laryngospasm.

Variable	Odds Ratio (95% CI)	
	Total Sample (n=8,282)	Prospective Subset (n=6,289)
Age <2 y*	1.41 (0.47–4.26)	1.59 (0.51–4.95)
Age ≥13 y*	0 [†]	0 [†]
Low intramuscular dose [†]	0 [†]	0 [†]
High intravenous dose [†]	2.15 (0.78–5.86)	3.72 (1.28–10.8)
Oropharyngeal procedure	3.75 (1.07–13.07)	2.21 (0.48–10.1)

The area under the model receiver operator curve is 0.595. The model demonstrated satisfactory goodness of fit, with the Hosmer-Lemeshow $P=.232$. Findings were essentially identical for the prospective subset.

*Reference group aged 2 to <13 years.

[†]There were no observations of laryngospasm in these patient subsets.

[‡]Reference group children without low intramuscular or high intravenous dosing.

support characteristic of this drug may make it preferable to other sedatives in children with substantial underlying illness.⁶⁰ Our data support this latter premise because ASA class greater than or equal to 3 was not associated with any significantly greater risk of airway and respiratory adverse events. Of the 92 such children with higher ASA status, there were no occurrences of apnea and only 1 occurrence of laryngospasm.

The relative safety of ketamine by the intravenous or intramuscular route has been a source of debate^{27,60,73} and has been studied in 1 controlled trial.²⁷ Although our unadjusted comparisons demonstrate an increased risk of airway and respiratory adverse events with the intravenous route relative to intramuscular, this effect was no longer significant when controlling for other variables, including the use of high intravenous dosing. Thus, as long as high intravenous dosing is avoided, our data suggest similar risk between these 2 routes of administration.

The coadministration of atropine or glycopyrrolate has traditionally been recommended with ketamine to mitigate hypersalivation and its associated risk of airway and respiratory adverse events.⁶⁰ Despite this, some emergency physicians

Table 5. Multiple logistic regression model of apnea.

Variable	Odds Ratio (95% CI)	
	Total Sample (n=8,282)	Prospective Subset (n=6,289)
Age <2 y*	1.63 (0.81–3.30)	1.58 (0.76–3.27)
Age ≥13 y*	2.86 (1.43–5.73)	3.26 (1.49–7.14)
Low intramuscular dose [†]	0 [†]	0 [†]
High intravenous dose [†]	5.11 (2.85–9.16)	10.7 (5.59–20.4)
Oropharyngeal procedure	2.41 (1.06–5.46)	1.33 (0.52–3.44)
ASA class ≥3	0 [†]	0 [†]
Intravenous route (relative to intramuscular)	2.26 (0.85–5.99)	1.48 (0.50–4.40)
Anticholinergic	2.06 (1.11–3.84)	1.33 (0.68–2.62)
Benzodiazepine	1.71 (0.95–3.05)	2.26 (1.22–4.21)

The area under the model receiver operator curve is 0.778. The model demonstrated satisfactory goodness of fit, with the Hosmer-Lemeshow $P=.734$.

*Reference group aged 2 to <13 years.

[†]Reference group children without low intramuscular or high intravenous dosing.

[†]There were no observations of apnea in these patient subsets.

regularly omit such adjunctive therapy without apparent problem.³¹ Indeed, an anticholinergic was used in only 65% of children in the current aggregate sample. A surprising finding in our study was that overall airway and respiratory adverse events (but not the subsets of laryngospasm or apnea) were significantly higher—not lower—in the group receiving concurrent anticholinergics. This was true in both the simple comparison and after adjusting for the other variables, with all findings unequivocal. Given the potential confounding influence of age on this factor,³¹ we repeated our analyses, adjusting for age as a continuous rather than categorical variable, but again confirmed this same outcome. We are unable to explain the basis for this paradoxical result, which is the opposite of conventional wisdom. Regardless, our data are statistically robust and do not support the regular or routine use of such adjunct agents.

Two ED randomized controlled trials of ketamine with and without midazolam have shown no measurable benefit to such adjunctive therapy to prevent emergency reactions,^{6,52} and one of the 2 showed greater oxygen desaturation with midazolam.⁵² Our data strongly support the concept that overall airway and respiratory adverse events, particularly apnea, are significantly more frequent when benzodiazepines are coadministered. Although it is possible that some subsets of children may benefit from prophylactic benzodiazepines,⁷⁴ there are currently no criteria to identify these children.

In summary, risk factors for ketamine-associated airway and respiratory adverse events are high intravenous doses, administration to children younger than 2 years or aged 13 years or older, and the use of coadministered anticholinergics or benzodiazepines. Such risk is not independently altered by route (intravenous versus intramuscular), oropharyngeal procedures, or underlying physical illness. This information can be used to help risk-stratify children before ED sedation and guide ketamine administration technique. Our data do not support

the regular or routine use of anticholinergics or benzodiazepines, although the effect of these agents on emesis and unpleasant recovery reactions was not studied.

Supervising editors: Kathy N. Shaw, MD, MSCE; Michael L. Callahan, MD.

Drs. Shaw and Callahan were the supervising editors on this article. Dr. Green did not participate in the editorial review or decision to publish this article.

Author contributions: SMG conceived and designed the study. The methodology was critiqued and revised with extensive input from MGR, BK, LB, DA, RDP, JEW, and GT. All authors reviewed and recoded their data to comply with study definitions, and before data analysis the study protocol was critiqued and refined by all authors. SMG performed the data analysis, and a writing committee composed of SMG, MGR, and BK then created the article. All authors critiqued the draft, and there were substantial revisions. SMG takes responsibility for the paper as a whole.

Funding and support: By *Annals* policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article that might create any potential conflict of interest. The authors have stated that no such relationships exist. See the Manuscript Submission Agreement in this issue for examples of specific conflicts covered by this statement.

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Publication dates: Received for publication August 23, 2008. Revisions received October 22, 2008, and November 18, 2008. Accepted for publication December 9, 2008. Available online February 7, 2009.

Reprints not available from the authors.

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APPENDIX:

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Appendix E1. Association of clinical variables with airway/respiratory adverse events

Characteristic	Airway Adverse Event (n=319)	No Airway Adverse Event (n=7,963)	Difference (95%CI)
Age (years)	Mean 6.7 Median 5.5 IQR 2.4, 10.6	Mean 6.4 Median 5.6 IQR 3.0, 9.1	0.3 (-0.2, 0.7)
Age group			
<2 years	60 (6.3%)	889 (93.7%)	
2 to <13 years	205 (3.1%)	6,434 (96.9%)	
≥13 years	54 (7.8%)	640 (92.2%)	
IV route	256 (80.3%)	5,421 (68.1%)	12.2% (7.7%, 16.6%)
Initial IM dose ^a	Mean 3.5 Median 4.0 IQR 3.2, 4.1	Mean 3.5 Median 3.9 IQR 2.5, 4.0	0.03 (-0.26, 0.31)
Total IM dose ^b	Mean 3.8 Median 4.0 IQR 3.6, 4.1	Mean 3.8 Median 4.0 IQR 2.9, 4.1	0 (-0.3, 0.4)
Initial IV dose ^c	Mean 1.7 Median 1.2 IQR 1.0, 2.5	Mean 1.6 Median 1.1 IQR 1.0, 1.9	0.1 (0, 0.3)
Total IV dose ^d	Mean 2.9 Median 1.8 IQR 1.0, 3.8	Mean 2.1 Median 1.5 IQR 1.0, 2.5	0.7 (0.5, 1.0)
Ketamine dose ^e			
Low IM	7 (1.0%)	675 (99.0%)	
High IV	67 (7.9%)	779 (92.1%)	
Other	245 (3.6%)	6,509 (96.4%)	
Oropharyngeal procedure	27 (8.5%)	241 (3.0%)	5.4% (2.4%, 8.5%)
ASA ≥3	5 (1.6%)	87 (1.1%)	0.5% (-0.9%, 1.9%)
Anticholinergic	242 (75.9%)	5,438 (68.3%)	7.6% (2.8%, 12.4%)
Benzodiazepine	158 (49.5%)	2,582 (32.4%)	17.1% (11.5%, 22.7%)

^aIncludes the 2,453 IM sedations with documented initial doses, of which there were 53 airway / respiratory adverse events.

^bIncludes all 2,604 IM sedations of which there were 63 airway / respiratory adverse events.

^cIncludes the 4,293 IV sedations with documented initial doses, of which there were 223 airway / respiratory adverse events.

^dIncludes all 5,678 IV sedations of which there were 256 airway / respiratory adverse events.

^eLow IM dose is a total dose <3.0 mg/kg IM. High IV dose is an initial dose ≥2.5 mg/kg IV or total dose ≥5.0 mg/kg IV.

Appendix E2. Association of clinical variables with laryngospasm

Characteristic	Laryngospasm (n=22)	No Laryngospasm (n=8,260)	Difference (95%CI)
Age (years)	Mean 3.8 Median 3.7 IQR 2.4, 4.9	Mean 6.4 Median 5.6 IQR 3.0, 9.1	-2.6 (-0.9, -4.3)
Age group			
<2 years	4 (0.4%)	945 (99.6%)	
2 to <13 years	18 (0.3%)	6,621 (99.7%)	
≥13 years	0 (0%)	694 (100%)	
IV route	10 (45.5%)	5,667 (68.6%)	-23.2% (-44.0, -2.3%)
Initial IM dose ^a	Mean 3.8 Median 4.0 IQR 3.7, 4.1	Mean 3.5 Median 3.9 IQR 2.5, 4.0	0.3 (-1.0, 0.3)
Total IM dose ^b	Mean 4.0 Median 4.0 IQR 3.7, 4.1	Mean 3.8 Median 4.0 IQR 2.9, 4.1	0.2 (-1.0, 0.6)
Initial IV dose ^c	Mean 2.0 Median 1.5 IQR 1.0, 2.9	Mean 1.6 Median 1.1 IQR 1.0, 2.0	-0.4 (-1.0, 0.2)
Total IV dose ^d	Mean 3.8 Median 3.5 IQR 1.5, 5.0	Mean 2.1 Median 1.5 IQR 1.0, 2.5	-1.7 (-2.8, -0.6)
Ketamine dose ^e			
Low IM	0 (0%)	682 (100%)	
High IV	5 (0.6%)	841 (99.4%)	
Other	17 (0.3%)	6,737 (99.7%)	
Oropharyngeal procedure	3 (13.6%)	265 (3.2%)	10.4% (-3.9%, 24.8%)
ASA ≥3	1 (4.5%)	91 (1.1%)	3.4% (-5.3%, 12.2%)
Anticholinergic	16 (72.7%)	5,438 (65.8%)	6.9% (-14.5%, 22.8%)
Benzodiazepine	12 (54.5%)	2,728 (33.0%)	21.5% (0.7%, 42.4%)

^aIncludes the 2,453 IM sedations with documented initial doses, of which there were 10 laryngospasms.

^bIncludes all 2,604 IM sedations of which there were 12 laryngospasms.

^cIncludes the 4,293 IV sedations with documented initial doses, of which there were 9 laryngospasms.

^dIncludes all 5,678 IV sedations of which there were 10 laryngospasms.

^eLow IM dose is a total dose <3.0 mg/kg IM. High IV dose is an initial dose ≥2.5 mg/kg IV or total dose ≥5.0 mg/kg IV.

Appendix E3. Association of clinical variables with apnea

Characteristic	Apnea (n=63)	No Apnea (n=8,219)	Difference (95%CI)
Age (years)	Mean 7.3 Median 7.0 IQR 2.7, 10.8	Mean 6.4 Median 5.6 IQR 3.0, 9.1	-0.9 (-1.9, 0.1)
Age group			
<2 years	11 (1.2%)	938 (98.8%)	
2 to <13 years	41 (0.6%)	6,598 (99.4%)	
≥13 years	11 (1.6%)	683 (98.4%)	
IV route	58 (92.1%)	5,619 (68.4%)	23.7% (16.9%, 30.4%)
Initial IM dose ^a	Mean 2.7 Median 3.0 IQR 1.2, 4.1	Mean 3.5 Median 3.9 IQR 2.5, 4.0	-0.8 (-1.8, 0.2)
Total IM dose ^b	Mean 3.9 Median 3.8 IQR 3.8, 4.1	Mean 3.8 Median 4.0 IQR 2.9, 4.1	0.1 (-1.1, 1.3)
Initial IV dose ^c	Mean 2.2 Median 2.6 IQR 1.0, 3.1	Mean 1.6 Median 1.1 IQR 1.0, 1.9	0.6 (-0.3, 0.9)
Total IV dose ^d	Mean 3.3 Median 1.6 IQR 1.0, 4.2	Mean 2.1 Median 1.5 IQR 1.0, 2.5	1.1 (-0.7, 1.6)
Ketamine dose ^e			
Low IM	0 (0%)	682 (100%)	
High IV	27 (3.2%)	819 (96.8%)	
Other	36 (0.5%)	6,737 (99.5%)	
Oropharyngeal procedure	8 (12.7%)	260 (3.2%)	9.5% (1.3%, 17.8%)
ASA ≥3	0 (0%)	92 (1.1%)	-1.1% (-1.3%, 0.1%)
Anticholinergic	46 (73.0%)	5,634 (68.5%)	4.5% (-6.5%, 15.5%)
Benzodiazepine	41 (65.1%)	2,699 (32.8%)	32.2% (20.4%, 44.1%)

^aIncludes the 2,453 IM sedations with documented initial doses, of which there were 4 apneas.

^bIncludes all 2,604 IM sedations of which there were 5 apneas.

^cIncludes the 4,293 IV sedations with documented initial doses, of which there were 50 apneas.

^dIncludes all 5,678 IV sedations of which there were 58 apneas.

^eLow IM dose is a total dose <3.0 mg/kg IM. High IV dose is an initial dose ≥2.5 mg/kg IV or total dose ≥5.0 mg/kg IV.

Appendix E4. Ketamine dosing and airway/respiratory adverse events in the subset of children ≥13 years

Characteristic	Airway		Difference (95%CI)
	Adverse Event	No Airway Adverse Event	
Initial IM dose (n=3/37)	Mean 3.3 Median 4.0 IQR 1.9, 4.0	Mean 3.5 Median 3.8 IQR 3.0, 4.0	-0.2 (-1.2, 0.9)
Total IM dose (n=4/40)	Mean 3.4 Median 4.0 IQR 3.0, 4.0	Mean 3.6 Median 3.8 IQR 3.2, 4.0	-0.2 (-1.3, 1.0)
Initial IV dose (n=41/457)	Mean 1.4 Median 1.0 IQR 1.0, 1.5	Mean 1.4 Median 1.0 IQR 1.0, 1.6	0 (-0.3, 0.3)
Total IV dose (n=50/600)	Mean 2.0 Median 1.2 IQR 1.0, 1.9	Mean 1.7 Median 1.3 IQR 1.0, 2.0	0.3 (-0.1, 0.7)

Appendix E5. Ketamine dosing by age strata

Dose	Age <2 years	Age 2 to <13 years	Age ≥13 years
Initial IM dose (n=429/1,984/40)	Mean 3.4	Mean 3.5	Mean 3.5
Median 3.9	Median 3.9	Median 3.8	
IQR 2.5, 4.0	IQR 2.5, 4.0	IQR 3.0, 4.0	
Total IM dose (n=458/2,102/44)	Mean 3.9	Mean 3.8	Mean 3.6
Median 4.0	Median 4.0	Median 3.9	
IQR 3.0, 4.2	IQR 2.9, 4.1	IQR 3.2, 4.0	
Initial IV dose (n=397/3,398/498)	Mean 1.7	Mean 1.6	Mean 1.4
Median 1.4	Median 1.1	Median 1.0	
IQR 1.0, 2.0	IQR 1.0, 2.0	IQR 1.0, 1.6	
Total IV dose (n=491/4,537/650)	Mean 2.9	Mean 2.1	Mean 1.8
Median 2.0	Median 1.5	Median 1.3	
IQR 1.2, 3.8	IQR 1.0, 2.5	IQR 1.0, 2.0	