Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: an individual-patient data meta-analysis of 8,282 children


CRD summary
This review concluded that patients sedated with ketamine were at higher risk of airway and respiratory adverse events if they were younger than 21 years, or if physicians used co-administered anticholinergics or benzodiazepines. The quality and variability of raw data, and potential biases arising from the review and analytical methods, result in considerable uncertainty about the reliability of the conclusions.

Authors' objectives
To identify clinical factors predictive of uncommon airway and respiratory adverse events in children admitted to emergency departments and sedated with ketamine

Searching
PubMed was searched (1966 to May 2008) with no language restriction. Search terms were reported. Reference lists of identified articles were also checked for further studies. Authors were contacted to identify any missing studies.

Study selection
Prospective and retrospective observational case series of parenteral ketamine administrations in children (up to 21 years old) for procedural sedation in an emergency department setting were eligible for inclusion in the review. Studies were excluded if they had no individual patient data (IPD) available, had fewer than 20 patients, had no measure of dose for each individual, or were propofol was co-administered.

The primary outcome was airway or respiratory adverse event (upper airway obstruction, stridor, hypoventilation or oxygen desaturation that resolved with repositioning of the airway). Secondary outcomes were laryngospasm (evidence of airway obstruction unresolved by airway alignment procedures) and apnoea (cessation of spontaneous respiration considered significant by observers or decrease in oxygen saturation to 90% or less).

In included trials, predictor variables were ketamine route (intravenous versus intramuscular administration); ketamine initial dose; ketamine total dose; presence or absence of co-administered anticholinergics; presence or absence of co-administered benzodiazepines; patient age; American Society of Anesthesiologists (ASA) physical status; and presence or absence of oropharyngeal procedural indication (coded as present versus absent). The median age of patients was 5.6 years. The median initial dose of ketamine administered was 3.9mg. Most included patients had an ASA physical status of class 1 or 2.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
IPD were obtained and checked for missing data. Prospective and retrospective analyses were distinguished, but the authors did not state how consistency between IPD and aggregate data was assessed, or how the quality of case series was further distinguished.

The authors did not state how many reviewers performed the validity assessment

Data extraction
IPD were obtained from the case series reporting outcomes and covariates according to study definitions provided by the authors.

The authors did not state how many reviewers performed the data extraction.
Methods of synthesis
Multiple logistic regression was performed for each of the three adverse outcomes. Covariate selection was based on the authors’ clinical judgement of biological plausibility; the number of covariates was restricted to 10% of the number of event outcome observations. Model fit was assessed using Hosmer-Lemeshow (HL) tests and area under receiver operating characteristic curves (AUR).

Sensitivity analyses were performed on retrospective and prospective studies, and using age as a continuous and categorical predictor.

Results of the review
Thirty-two case-series were identified consisting of 8,353 patients, of which 71 individual sedations were excluded as not fulfilling inclusion criteria.

The overall rate of airways adverse events was 3.82%, but this varied across case series from less than 1% to over 26%.

Overall incidence of airway and respiratory adverse events was associated with: initial dose of over 2.5mg/kg or total dose of over 5mg/kg of ketamine (odds ratio/OR 2.18, 95% confidence interval/CI 1.59 to 2.99); presence of co-administered anticholinergics (OR 1.82, 95% CI 1.36 to 2.42); presence of co-administered benzodiazepines (OR 1.39, 95% CI 1.08 to 1.78); children younger than two years (OR 2.0, 95% CI 1.47 to 2.72); and children of 13 years or older (OR 2.72, 95% CI 1.97 to 3.75). Overall incidence of airways and respiratory adverse events were not statistically significant for American Society of Anesthesiologists (ASA) physical status, and intravenous versus intramuscular ketamine administration.

Oropharyngeal procedural indication was significant for overall incidence (OR 2.01, 95% CI 1.29 to 3.12), but the effect was smaller and not statistically significant in the prospective studies subset (OR 1.30, 95% CI 0.77 to 2.18). These results were invariant to recoding of age as a continuous variable (results not reported).

Differences between total sample and prospective studies were detailed in the review.

Odds ratios were also reported for laryngospasm and apnoea for the total sample and prospective subsets.

Overall model fit was poor (AUR 0.687, HL p=0.001), with some improvement for laryngospasm (AUR 0.595, HL p=0.232), and a reasonable fit for apnoea (AUR 0.778, HL p=0.734).

Results for secondary outcomes were presented in the review.

Authors’ conclusions
The risk factors that predicted uncommon airway and respiratory adverse events in children admitted to emergency departments and sedated with ketamine were high intravenous doses, administration to patients younger than two years or between 13 and 21 years, and the use of co-administered anticholinergics or benzodiazepines.

CRD commentary
The authors addressed a clear research question, supported by appropriate inclusion criteria; they used an IPD approach advocated as gold standard in evidence synthesis. However, a single database was searched using a limited range of search terms. Methods used to reduce error and bias during study selection were not reported.

The authors did report that missing data were checked and distinguished prospective and retrospective studies, but assessments of the quality and consistency of data were not reported. The sensitivity of the results to covariate selection based on the authors’ judgement of biological plausibility was unclear. The analysis did not appear to stratify by study, resulting in high potential for confounding; the primary model had discriminatory power only slightly better than chance.

The authors acknowledged limitations in the high heterogeneity of the collated studies, nature of observational data, model fit, lack of other potentially important covariates, distributional assumptions, and variation in definition of
events. Overall, these problems result in uncertainty regarding the reliability and robustness of both results and conclusions.

**Implications of the review for practice and research**

**Practice**: The authors stated that physicians using ketamine for sedation in a paediatric setting may wish to rethink their intravenous dosing strategy and use of concurrent anticholinergics or benzodiazepines.

**Research**: The authors stated that future research should target specific adverse events rather than aggregating them into a heterogeneous global category.

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