Predictors of emesis and recovery agitation with emergency department ketamine sedation: an individual-patient data meta-analysis of 8,282 children


CRD summary
This individual patient analysis suggested that there might be a higher risk of emesis for patients sedated with ketamine if they were young adolescents or physicians used an initial dose of ≥2.5mg/kg or total dose of ≥5mg/kg. Low quality variable raw data and potential biases from the search and analytical methods caused considerable uncertainty about the reliability of the conclusions.

Authors' objectives
To identify factors predictive of emesis and recovery agitation in children admitted to emergency departments and sedated with ketamine.

Searching
MEDLINE was searched (1966 to May 2008) without language restrictions. Search terms were reported. Reference lists of identified articles were 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 (≤21 years) for procedural sedation in an emergency department setting were eligible for inclusion in the review.

The outcomes were emesis (an episode of vomiting during sedation or recovery before discharge) recovery agitation (any combination of agitation, crying, hallucinations and nightmares) and clinically important agitation (agitation leading to treatment or described as severe by investigators).

Predictor variables were intravenous versus intramuscular administration, initial dose, 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).

Two additional dichotomisations of ketamine technique were low dose (<3mg/kg) and high dose (initial dose ≥2.5mg/kg or total dose ≥ 5mg/kg) which had significant effects on respiratory adverse effects reported elsewhere (see Other Publications of Related Interest).

Exclusion criteria (described in the reference cited in Other Publications of Related Interest) were: no individual patient data (IPD) available; fewer than 20 patients; no measure of dose for each individual; and co-administration of propofol.

The median age of patients was 5.6 years. Median initial dose of ketamine was 3.9mg. Most of the included patients had an ASA physical status of one or two.

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. 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 and the number of covariates was restricted to 10% of the number of event outcome observations. Model fit was assessed using Hosmer-Lemeshow tests (HL) and area under receiver operating characteristic curves (AUR). Sensitivity analyses were performed on retrospective and prospective studies and use of age as a continuous and categorical predictor.

**Results of the review**

Thirty-two case-series were identified consisting of 694 episodes of emesis of 8,282 sedations and 630 cases of recovery agitation of 8,238 sedations. Overall rates of emesis were 8.4%, recovery agitation 7.6% and clinically important recovery agitation 1.4%.

Overall incidence of emesis was associated with initial dose ≥2.5mg/kg or total dose 5mg/kg (odds ratio 3.42, 95% confidence interval 2.54 to 4.61), age (odds ratio 1.15, 95% confidence interval 1.13 to 1.18). Odds ratios of <1 where 95% confidence intervals did not overlap 1 were reported for ASA score ≥3, intravenous route and co-administered anticholinergic and benzodiazepines.

Additional covariates where odds ratios exceeded 1 and 95% confidence intervals did not overlap 1 were low dose and total dose for recovery agitation and age and low dose for clinically important recovery agitation. An odds ratios of <1 where 95% confidence intervals did not overlap 1 was reported for intravenous route comparing odds of recovery agitation. Odds ratios were presented for the prospective subset of patients and where 95% confidence intervals overlapped 1.

Model fit was moderate (emesis AUR 0.695, HL p=0.588; recovery agitation AUR 0.637, HL p=0.997; clinically important recovery agitation AUR 0.624, HL p=1.00).

**Authors’ conclusions**

Predictors of ketamine-associated emesis were high initial dose (≥2.5mg/kg or total dose ≥5mg/kg) and age (peak at 12 years). There were no predictors for clinically important recovery agitation.

**CRD commentary**

The authors addressed a clear research question supported by appropriate inclusion criteria and used an IPD approach advocated as gold standard in evidence synthesis.

Only a single electronic source was searched. The range of search terms was limited. Methods used to reduce error and bias during study selection and data extraction were not fully reported. The authors reported that missing data were checked and distinguished prospective and retrospective studies. Assessments of the validity 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 account for correlation between the multiple outcomes. It was unclear how within-study and between-study treatment covariate interactions were pooled, which resulted in high potential for confounding. These problems engendered high uncertainty regarding the reliability and robustness of 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 tailor their sedation practice to particular patients and situations.
Research: The authors did not state any implications for research.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.