Adverse events associated with ketamine for procedural sedation in adults

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CRD summary
The review concluded that when ketamine was used for procedural sedation in adults, cardiorespiratory adverse events were rare but dysphoric emergence phenomena occurred in 10% to 20% patients and there was a likelihood of airway obstruction. The reliability of the authors’ conclusions is uncertain due to review process limitations and uncertain quality and design of the many included studies.

Authors' objectives
To evaluate the safety of the use of ketamine for procedural sedation in adults.

Searching
PubMed, EMBASE, TOXNET (to May 2006) and The Cochrane Library were searched for publications in English, Spanish, Russian, French, Portuguese and German; search terms were reported. Australian Adverse Drug Reactions Bulletin, European Public Assessment Reports from European Medicines Evaluation Agency, FDA Safety Information and Adverse Events Reporting Program and UK Current Problems in Pharmacovigilance were searched, as were selected books and review articles in the fields of emergency medicine, anaesthesiology, and clinical pharmacology literature and bibliographies of included articles. Selected experts in the field were contacted for unpublished studies.

Study selection
Trials that evaluated adverse effects of the use of ketamine to facilitate the performance of painful procedures were eligible for inclusion. Trials needed to use a dose of at least 1mg/kg intravenous or at least 2mg/kg intramuscular ketamine over a 30 minute period in spontaneously breathing adult patients with no continuous co-therapies.

Paediatric studies were defined as studies in which more than half of the patients were younger than 18 years. Eligible studies had to report either psychiatric or cardio-respiratory adverse effects (the primary outcomes, for which detailed definitions were provided); rate of patient satisfaction with anaesthesia was allowed as a surrogate for a psychiatric adverse event. Trials of endotracheally intubated patients, trials of ketamine for other purposes, trials that used supplemental conduction anaesthesia, trials that did not study racemic ketamine, volunteer studies and trials that used other methods of ketamine administration were excluded (precise details were provided). Any foreign-language articles without an abstract and articles without an abstract that were not clearly relevant were excluded.

Most of the comparative studies were of gynaecological procedures. Most of the non-comparative studies were of non-specified major or minor surgery or various procedures, followed by gynaecological and emergency department procedures, field hospital surgery and plastic surgery. The authors considered that 83 studies were applicable to emergency medicine. Most studies were published in the 1970s. Studies had a global spread and a significant number were in Africa and Asia. Patient age ranged from six weeks to more than 100 years. Most studies used ketamine in addition to other drugs, sometimes after use of other drugs and often with later supplementary doses. Direct comparisons between drugs were made only between ketamine and placebo, diazepam, thiopental and nitrous oxide, thiopentone, methohexitone and lorazepam; details of doses and regimens used were provided. The authors stated that many of the drugs used with ketamine were no longer available.

The authors did not report how many reviewers performed study selection; the initial screen for relevance was performed by one reviewer.

Assessment of study quality
Criteria relevant to study quality were extracted: study design and setting; details of the intervention; and possible confounders. No formal quality assessment was performed.

Data extraction
Data were extracted using an abstraction form. Numbers of adverse events for each outcome were extracted, sometimes
as percentages.

The authors did not report how many reviewers performed data extraction.

**Methods of synthesis**

A qualitative narrative synthesis was provided because contexts, end points and methodological quality of studies varied widely.

**Results of the review**

Eighty-seven studies were identified (n≥59,304, range one to 30,000) but the tables included only 86 studies: 26 comparative studies and 60 non-comparative studies. Most participants were included in the non-comparative studies. Fourteen of the comparative studies were randomised controlled trials (RCTs) and three of these were double-blind. In many studies all groups received the same ketamine regime; only 14 comparative studies (five RCTs) compared ketamine with other treatment regimes, different doses of ketamine, intravenous versus intramuscular ketamine or racemic ketamine.

Only one case of an adverse cardiorespiratory event was reported (a case report). Cardiostimulatory effects of ketamine were mitigated by sympatholytic agents in two comparative studies and a case report.

There were no reports of clinical indications of aspiration associated with ketamine; one small comparative study showed radiological evidence of contrast aspiration and also reported that ketamine patients maintained their pharyngeal reflexes, swallowing liquids if challenged. However, five non-comparative studies reported that ketamine patients required airway manoeuvres such as a chin-lift or jaw-thrust for positional obstruction. Laryngospasm was reported very rarely in adults and as either transient or responsive to bag-valve-mask ventilation (BVM) in two non-comparative studies and was considered not to be a risk in three other comparative studies of endoscopic (ear, nose and throat), dental and tonsillectomy procedures. Ketamine produced transient respiratory depression (sometimes included apnoea), usually within the first two to three minutes (five studies that included one small comparative study). Respiratory depression was more frequent when ketamine was used with concurrent agents known to depress respiration (four studies that included one comparative study where 40% and 60% patients required BMV and who received ketamine and midazolam at different doses versus none in the control group that received other drugs).

The rate of psychiatric adverse events associated with ketamine monotherapy ranged from 10% to 20% (seven studies that included six comparative studies and five RCTs). Sedating agents were effective in terminating and preventing ketamine emergence reactions (13 studies); environmental interventions also reduced such events (four studies). The incidence of vomiting associated with ketamine ranged from 5% to 15% (six studies that included an RCT). An evanescent patchy erythematous rash on the upper torso that required no treatment occurred with ketamine in 5% to 20% patients (four studies that included two comparative studies).

Other adverse events were reported.

**Authors' conclusions**

When ketamine was used for procedural sedation in adults, dysphoric emergence phenomena occurred in 10% to 20% patients. Providers must be prepared to recognise and manage airway obstruction, but cardiorespiratory adverse events were rare.

**CRD commentary**

The review addressed a well-defined question in terms of participants and relevant outcomes. There were no restrictions on type of study design or intervention that included ketamine. Relevant databases were searched in six languages. Unpublished studies were considered. Publication bias was not assessed. Although some criteria relevant to validity assessment were addressed, no formal study quality assessment was undertaken and so it was not possible to adequately comment on the reliability of the results presented. No efforts to reduce error and bias were reported. Relevant study details were provided, but no details of loss to follow-up were given. A qualitative narrative synthesis was provided due to the heterogeneity of study design and context of the studies, but details of the results were insufficient to enable the
reader to judge their significance. Most of the included studies were non-comparative in design and so liable to bias.

The authors’ conclusions reflected the evidence presented, but limitations in the review process, potential biases in the included studies and a lack of quality assessment made the reliability of the conclusions uncertain.

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

**Practice:** The authors described many implications for practice and these included: apnoea seemed more likely with large intravenous ketamine boluses administered rapidly so should be dosed according to ideal body weight and infused for one to two minutes; and patients with known severe atherosclerotic heart disease may not be appropriate for ketamine or any procedural sedation.

**Research:** The authors stated that given ketamine’s low adverse event rate it was unlikely that a prospective trial of sufficient size would be performed.

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