Does ketamine have a role in managing severe exacerbation of asthma in adults?

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Authors’ objectives
To evaluate the role of ketamine in the management of severe exacerbation of asthma in adults.

Searching
MEDLINE (from January 1966 to September 2000), EMBASE (from January 1988 to September 2000) and the Cochrane Database of Systematic Reviews (Issue 2, 2000) were searched for publications in the English language, using the search terms 'ketamine', 'status asthmaticus' and 'asthma'. The references in relevant literature were also examined.

Study selection
Study designs of evaluations included in the review
All articles of any study design were eligible for inclusion in the review.

Specific interventions included in the review
Ketamine therapy comprised 0.75 mg/kg intravenous (i.v.) bolus, then 0.75 mg/kg i.v. over 10 minutes followed by 0.15 mg/kg/hour infusion for 1 to 8 hours; 2.5 mg/kg/hour infusion for 26 hours; 20 mg i.v. then 5 microg/kg/minute for 18 hours; or three i.v. bolus over 75 minutes. In the one included controlled trial, ketamine 0.2 mg/kg i.v. bolus and an infusion of 0.5 mg/kg/hour for 3 hours was added to conventional asthma therapy and compared with placebo added to the same conventional asthma therapy. Conventional asthma therapy included oxygenation, nebulised albuterol (0.5 mg every 20 minutes), and intravenous sodium succinate (125 mg) followed by continuous nebulised albuterol (10 mg/hour).

Participants included in the review
Adults aged 18 to 65 years with severe acute exacerbation of asthma were included in the controlled trial. Acute asthma exacerbation was defined as a peak expiratory flow rate (PEFR) of less than 40% of the predicted value after 3 courses of therapy with nebulised albuterol, 0.5 mg in 2.5 mL saline solution. Patients with chronic obstructive disease, emergency intubation, hypertension, coronary artery disease, hyperthyroidism, pregnancy, psychiatric disorders, inability to perform bedside spirometry, or allergy to ketamine were excluded from the study. The case reports included patients with the following: acute severe asthma unresponsive to conventional therapy; respiratory arrest; refractory severe asthma complicated by acute myocardial infarction; and severe asthma. Articles discussing ketamine administered for analgesia, sedation, rapid-sequence intubation, and non-asthma-related bronchospasm were excluded.

Outcomes assessed in the review
The clinical end points included spirometry testing (forced expiratory volume in 1 second, i.e. FEV1, and PEFR), oxygen saturation, arterial blood gases (pH, partial arterial oxygen pressure and partial arterial carbon dioxide pressure), length of stay, hospital admission where applicable, and adverse effects.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.
Data from the randomised controlled trial (RCT) were extracted in the categories: sample size, age, illness, treatment, control, results, and drop-outs. Data from the case reports were extracted in the categories: age, pre-ketamine interventions, ketamine therapy, results, and adverse effects.

**Methods of synthesis**

**How were the studies combined?**
The RCT and the case reports were discussed separately in a narrative commentary.

**How were differences between studies investigated?**
Differences between the studies were mentioned in the text.

**Results of the review**

One RCT (n=53) and 5 case reports were included.

In the RCT, no statistically-significant difference was seen between the treatment groups in terms of FEV1, PEFR, Borg visual analogue scale for dyspnoea, respiratory rate and hospital admission. Adverse effects were higher in the ketamine group than the placebo group: 17.4 and 4.8%, respectively (p=0.1880). The most common adverse effects were dysphoria and dizziness.

In the case reports, all patients with refractory severe exacerbation of asthma requiring mechanical ventilation appeared to receive some benefit from ketamine, with alleviation of bronchospasm and improved oxygenation. Adverse effects of hallucinations, extracorporeal sensations and increased pulmonary secretions were reported.

**Authors’ conclusions**

There was limited evidence in the literature to support the administration of ketamine in severe exacerbation of asthma. A few cases suggested a possible benefit from ketamine, but it should not be considered until controlled clinical trials demonstrate that the benefits outweigh the risks for patients for whom other standard therapies failed.

**CRD commentary**

The research question posed by this review was clear, and the study selection criteria imposed were appropriate to answer this question. The literature search was reasonable. However, the search terms used were limited and the restriction to English language publications may have resulted in some studies being missed. No attempt was made to find unpublished research. A validity assessment was not conducted but, given that only one RCT (which was stated to be double-blind) and five case reports were found, this is probably not an issue. Sufficient details of the included studies were provided, and the type of synthesis was appropriate given the different types of research. However, it is unclear how valuable case reports can be in determining the effectiveness of an intervention, and although they have been given less weight than the RCT, they should perhaps have been reported less fully than they are. The authors acknowledge the likelihood that only case reports of positive results from ketamine would be published. The authors’ cautiously positive conclusions of there being 'limited evidence to support administration of ketamine' were based on the case reports only and seem to favour ketamine. The results of the review, however, would suggest no evidence to support ketamine, other than perhaps in a trial in mechanically-ventilated patients.

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

**Practice:** The authors state that ketamine should not be routinely administered to nonintubated patients with severe exacerbation of asthma in the emergency department.

**Research:** The authors suggest that controlled clinical trials are needed to determine the efficacy and safety of ketamine in patients who have not had success with other standard therapies, and the appropriate dosage and duration of therapy.

**Reviewer’s statement:** The only potential benefits of ketamine seen in this review were in mechanically ventilated
patients, so future research should perhaps be restricted to this patient group.

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