Ketamine for management of acute exacerbations of asthma in children (Review)

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[Intervention Review]

Ketamine for management of acute exacerbations of asthma in children

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ABSTRACT

Background

Asthma is the most common chronic disease in children, and children with asthma frequently visit the paediatric emergency departments with acute exacerbations. Some of these children fail to respond to standard therapy (aerosol beta$_2$-agonist with or without aerosol anticholinergic and oral or parenteral corticosteroids) for acute asthma leading to prolonged emergency department stay, hospitalisation, morbidity (e.g. barotrauma, intubation) and death, albeit rarely. Ketamine may relieve bronchospasm and is a potentially promising therapy for children with acute asthma who fail to respond to standard treatment.

Objectives

To evaluate the efficacy of ketamine compared to placebo, no intervention or standard care for management of severe acute asthma in children who had not responded to standard therapy.

Search methods

We identified trials from the Cochrane Airways Group Specialised Register of trials (CAGR) and ClinicalTrials.gov. We reviewed reference lists of all primary studies and review articles for additional references. We contacted authors of identified trials and asked them to identify other published and unpublished studies. The latest search was in July 2012.

Selection criteria

Randomised controlled trials comparing ketamine to placebo or standard care in children (up to 18 years of age) presenting with an acute asthma exacerbation who had not responded to standard therapy.

Data collection and analysis

Two review authors independently selected studies. The data were extracted in pre-defined proforma and were analysed independently by two review authors. The data analysis was performed using Review Manager 5.1.

Main results

A single study enrolling 68 non-intubated children was found eligible for inclusion in review. The study had low or unclear risk of bias. It demonstrated no significant difference in respiratory rate, oxygen saturation, hospital admission rate (odds ratio (OR) 0.77; 95% confidence interval (CI) 0.23 to 2.58) and need for mechanical ventilation between ketamine (0.2 mg/kg intravenous bolus over one

to two minutes, followed by a 0.5 mg/kg per hour continuous infusion for two hours) and placebo group. There were no significant side effects of ketamine in the study. There was also no difference in need for other adjuvant therapy (OR 2.19; 95% CI 0.19 to 25.40) and in Pulmonary Index Score (mean difference (MD) -0.40; 95% CI -1.21 to 0.41) between the groups.

Authors' conclusions

The single study on non-intubated children with severe acute asthma did not show significant benefit and does not support the case studies and observational reports showing benefits of ketamine in both non-ventilated and ventilated children. There were no significant side effects of ketamine. We could not find any trials on ventilated children. To prove that ketamine is an effective treatment for acute asthma in children, there is need for sufficiently powered randomised trials of high methodological quality with objective outcome measures of clinical importance. Future trials should also explore different doses of ketamine and its role in children needing ventilation because of severe acute asthma.

PLAIN LANGUAGE SUMMARY

Role of ketamine for management of acute severe asthma in children

Children frequently visit the emergency department for acute exacerbation of asthma. Some of these children fail to respond to standard treatment (corticosteroids and bronchodilators) with increased morbidity. Ketamine has bronchodilatory properties and may be useful for acute exacerbation of asthma. We evaluated the efficacy of ketamine for management of severe acute asthma in children who had not responded to standard therapy. We found, through systematic search, only one study where investigators assessed the usefulness of ketamine for management of severe acute asthma in children. While this single study suggested that there is a lack of evidence for usefulness of ketamine in acute exacerbation of asthma in children, more trials are needed regarding the use of ketamine in acute asthma before more specific recommendations can be made.

BACKGROUND

Description of the condition

Asthma is the most common chronic disease in children, with prevalence between 10% and 23% in the US (CDC 1996; Gergen 1988; NICE 2007). The prevalence and annual hospitalisation rates of asthma in children have increased from 1980 through the mid-1990s, to a plateau in the 2000s (Akinbami 2006; CDC 1996; Crane 1989; Sly 1999; Spitzer 1992). In the US, the annual hospitalisation rate for asthma among people aged 0 to 24 years was 16.8 per 10,000 population in 1980. This increased by 28% in 1993, reaching 21.4 per 10,000 (CDC 1996) and 27 per 10,000 in 2004 (Akinbami 2006). Approximately 3% of hospitalised asthmatic children respond poorly to treatment and require mechanical ventilation (Yung 1998). In children, a morality rate of 1.72 per 1000 hospitalised asthmatic patients has been reported (CDC 1996), with this trend declining in more recent years (Akinbami 2006). Although it is difficult to identify the criteria that may predict potentially fatal asthma in children, there are some risk factors that may suggest the possibility of severe, life-threatening asthma in children: these include: previous severe exacerbation, previous attack with respiratory failure, seizure or loss of consciousness, non-compliance to therapy, denial or failure to perceive severity of illness and dysfunctional family unit (Werner 2001).

The standard treatment of acute exacerbation of asthma in children includes O_2 supplementation, inhaled beta$_2$-agonist with or without ipratropium bromide (either through an inhaler and spacer device or nebulisation) and systemic corticosteroids (BTS 2009; GINA 2009; NHLBI 2007). However, there is limited evidence to guide the use of second-line therapies (e.g. aminophylline, magnesium sulphate, inhaled corticosteroids (ICS) or continuous intravenous (IV) infusion of beta$_2$-agonist) to treat children with acute severe exacerbation of asthma who respond poorly to standard treatment (BTS 2009; GINA 2009; NHLBI 2007).

Description of the intervention

Ketamine hydrochloride, a phencyclidine-derived agent, is a unique drug with anxiolytic, analgesic, amnesic and dissociative properties. It produces functional and electrophysiological disso-

ciation between the cortical and limbic systems of the brain, resulting in a cataleptic state (Green 1990). This trance-like cataleptic state is characterised by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respiration and cardiopulmonary stability (Green 2000). Ketamine has been used effectively and safely as an IV or intramuscular (IM) agent for procedural sedation and analgesia (PSA) in children both in emergency department (ED) and outpatient settings over many years (Ng 2002; Sobel 1999). It is used commonly to facilitate the completion of short painful procedures (e.g. suturing, lumbar puncture, removal of a foreign body) or reduction of children's fractures in the ED (McCarty 2000; Ng 2002). Finally, ketamine is the agent of choice in rapid sequence intubation for children and adults with severe respiratory distress (Brenner 2009; Burburan 2007; So 2001).

Ketamine is relatively safe in children and the side effects are generally mild (e.g. laryngospasm, emergency reactions, agitation) and self-limiting (Parker 1997; Roback 2005). The emergence reactions (confusion, delirium, excitement, hallucinations, irrational behaviour, agitation or pleasant dream-like state) may be observed often in older children (over 10 years old) and adults, but are very uncommon in younger children (Sherwin 2000).

How the intervention might work

Ketamine administration has been associated with an increase in pulmonary compliance (a measure of the ability of the lungs to distend, or swell, in response to pressure without disruption) and decrease in airway resistance in patients with obstructive airway disease (Betts 1971; Corssen 1972). Gateau et al reported that ketamine has a powerful bronchial relaxant effect and reversed the bronchoconstriction caused by histamine, acetylcholine, barium chloride or potassium chloride and the effect was not inhibited by propranolol and indomethacin, which excluded the involvement of beta activation and of prostaglandins (Gateau 1989). Ketamine is also known to inhibit catecholamine re-uptake processes and act as sympathomimetic agent resulting in bronchial relaxation (Cook 1991). One or all of the above mechanisms are responsible for bronchodilator effects of ketamine and probably play a role in the attenuation of bronchospasm in a patient with intrinsic asthma.

A number of case reports and case-control studies have reported improved relief from bronchospasm with use of ketamine in adults (Sarma 1992) and children with severe acute asthma, whether intubated or non-intubated (Betts 1971; Denmark 2006; Fischer 1977; Nehama 1996; Petrillo 2001; Rock 1986; Strube 1986; Youssef-Ahmed 1996).

Why it is important to do this review

Children with asthma frequently visit the ED with acute exacerbations. Some of these children fail to respond to standard therapy (aerosol beta$_2$-agonist with or without aerosol anticholinergic and oral or parenteral corticosteroid) for acute asthma leading to prolonged ED stays, hospitalisation, morbidity (e.g. barotrauma, intubation) and (albeit rarely) mortality. Ketamine may relieve bronchospasm and is a potentially promising therapy for children with acute asthma who do not respond to standard treatment.

OBJECTIVES

To evaluate the efficacy of ketamine as compared to placebo, no intervention or standard care for management of severe acute asthma in children who have not responded to standard therapy.

METHODS

Criteria for considering studies for this review

Types of studies

Prospective randomised controlled trials.

Types of participants

Children (up to 18 years of age) presenting with an acute asthma exacerbation who had not responded to standard therapy with aerosolised beta$_2$-agonist, with or without aerosolised anticholinergic drugs and oral or parenteral corticosteroid, for at least one hour.

We excluded studies enrolling adults only, non-randomised trials and cross-over trials. If we found studies that enrol both adults and children, we planned to request data of children from study investigators if such data were not presented separately in study.

Types of interventions

Use of IV or IM ketamine and comparison with placebo or intervention other than standard care or other adjuvant (second-line) therapy.

Types of outcome measures

Primary outcomes

1. Reduction in asthma severity parameters (e.g. respiratory rate, oxygen saturation, forced expiratory volume in one second (FEV1), peak expiratory flow rate (PEFR)).
2. Need for hospital admission.

3. Need for mechanical ventilation (non-invasive or invasive).
4. Adverse effects (especially emergency reactions).

Secondary outcomes

1. Need for other adjuvant therapy (e.g. magnesium sulphate, heliox, etc.).
2. Duration of ED (in hours) and hospital (in days) stay.
3. Change in asthma scoring system (PRAM - Pediatric Respiratory Assessment Measure) (Ducharme 2008); PASS - Pediatric Asthma Severity Score (Gorelick 2004) or PIS - Pulmonary Index Score (Scarfone 2000). We planned to combine results when the same scale was used in different studies.

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register of trials (CAGR), which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (Appendix 1). All records in the CAGR coded as 'asthma' were searched using the following terms: ketamin* or cyclohexan* or ketalar or ketaset or ketanest or kalipsol.

We also conducted a search of ClinicalTrials.gov. All databases were searched from their inception to July 2012 and there were no restriction on language of publication.

Searching other resources

We reviewed reference lists of all primary studies and review articles for additional references. We contacted authors of identified trials and ask them to identify other published and unpublished studies. We also contacted manufacturers and experts in the field, if required. In addition to the conference abstracts handsearched by the Cochrane Airways Group and included in the CAGR (Appendix 1), we also handsearched the abstracts from the Society of Academic Emergency Medicine (SAEM) and the Canadian Association of Emergency Physicians (CAEP) annual meetings from 2009 to 2012.

Data collection and analysis

Selection of studies

Two review authors (KRJ and DC) independently assessed for inclusion all of the potential studies that we identified as a result of the search strategy. Two review authors (KRJ and DC) then retrieved and independently assessed the full text of identified relevant studies for inclusion as per criteria mentioned. We corresponded with investigators, where appropriate, to clarify study eligibility. We listed excluded studies with reason of exclusion. We resolved any disagreement arising by discussion.

Data extraction and management

Two review authors (KRJ and DC) independently extracted data using a standardised data collection form in accordance with Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), which included the following data: source, eligibility, study methods, participants and settings, interventions and comparisons, outcomes, results, adverse outcomes and miscellaneous (e.g. funding source of the study or potential conflicts of interest). We recorded whether or not patients randomised to receive ketamine had already been given magnesium sulphate or heliox and whether use of these treatments was equal in both groups. Two review authors (KRJ and DC) independently extracted the data. We resolved any disagreement arising by discussion.

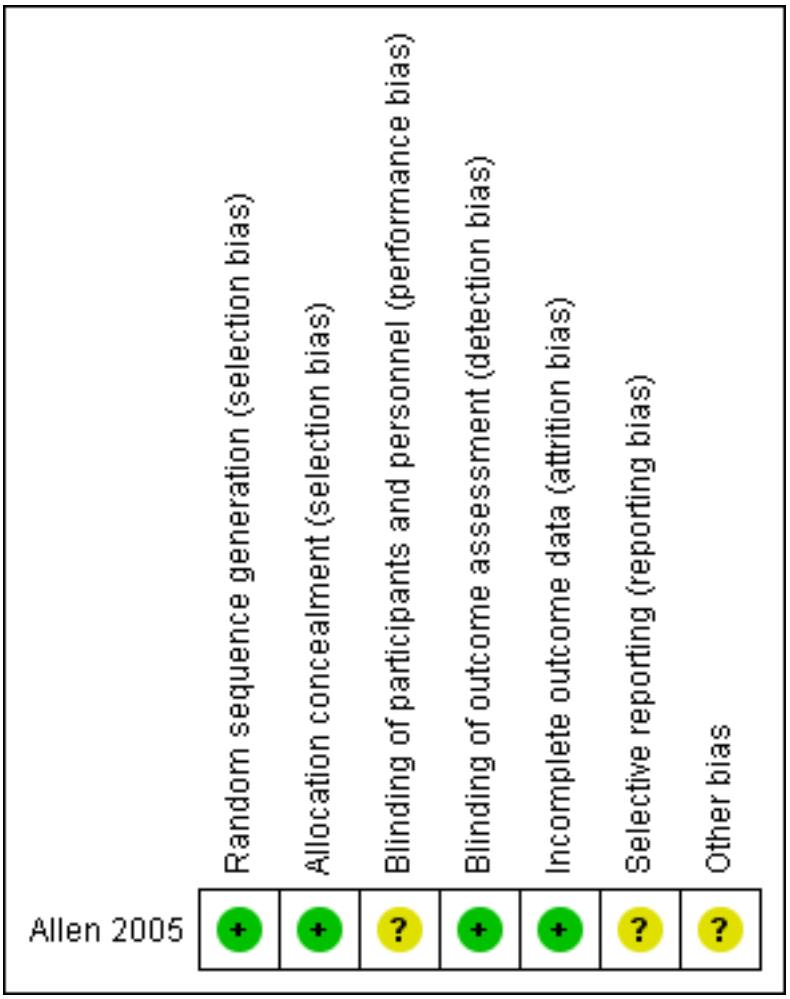
Assessment of risk of bias in included studies

Two review authors (KRJ and DC) independently assessed for risk of bias in included studies using the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion. We assessed the risk of bias according to the following domains.

1. Allocation sequence generation.
2. Concealment of allocation.
3. Blinding of participants and investigators.
4. Incomplete outcome data.
5. Selective outcome reporting.

We noted other sources of bias. We graded each potential source of bias as low, high or unclear risk of bias. We created a 'Risk of bias' summary figure (Figure 1) using Review Manager 5 (RevMan 2011).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Measures of treatment effect

We planned to analyse dichotomous outcome data by calculating the risk ratio (RR), odds ratio (OR) or risk difference (RD). We planned to express continuous outcome data as mean difference (MD) or standardised mean difference (SMD) if different scales were used for an outcome in different studies. We expressed the overall results with 95% confidence interval (CI).

Unit of analysis issues

We included only randomised controlled trials in the review. We excluded cross-over or cluster-randomised trials.

Dealing with missing data

We took the following steps to deal with missing data.

1. We contacted investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible.

2. We performed sensitivity analyses to assess how sensitive results were to reasonable changes in the assumptions that were made.

3. We addressed the potential impact of missing data on the findings of the review in the discussion section.

4. For missing standard deviations (SD) of continuous outcome data, we planned to calculate SD from study statistics (e.g. CI, standard errors, t values, P values, F values). If SD

calculation was still not possible, then we planned to impute it from other studies in meta-analysis as per details given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Where possible, we extracted data to allow an intention-to-treat (ITT) analysis, which aims to include all participants randomised into a trial irrespective of what happened subsequently. If there was a discrepancy in the number randomised and the numbers analysed in each treatment group, we calculated the percentage lost to follow-up and report this information.

Assessment of heterogeneity

We planned to assess clinical and methodological heterogeneity before pooling. We carried out assessment for statistical heterogeneity visually, using a Chi^2 test and using the I^2 statistic. Using the Chi^2 test, a P value < 0.1 (or a large Chi^2 statistic relative to its degree of freedom) provided evidence of heterogeneity of intervention effects (variation in effect estimates beyond chance). We interpreted the value of I^2 statistic as follows:

- 0% to 40% - might not be important;
- 30% to 60% - may represent moderate heterogeneity;
- 50% to 90% - may represent substantial heterogeneity;
- 75% to 100% - considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

Where we suspect reporting bias, we attempted to contact study authors asking them to provide missing outcome data. Where this was not possible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by a sensitivity analysis.

We planned to assess publication bias by funnel plots in Review Manager 5 (RevMan 2011), if sufficient numbers of included studies were available.

Data synthesis

We planned to carry out meta-analyses using Review Manager 5 (RevMan 2011). We planned to use a fixed-effect model for pooled data analysis and compare with a random-effects model in a sensitivity analysis and if there was important statistical heterogeneity among studies.

Subgroup analysis and investigation of heterogeneity

If sufficient data were available, we planned to conduct the following subgroup analyses:

1. children below five years and above five years of age;
2. moderate and severe exacerbation of asthma (as described in included studies);
3. different doses of ketamine (bolus or continuous infusion or bolus followed by continuous infusion and different doses of continuous infusion) and route of administration (IV or IM) of ketamine;
4. concurrent use of ICS or not.

We planned to use the following outcomes in subgroup analysis:

1. reduction in respiratory distress;
2. need for hospital admission;
3. need for mechanical ventilation;
4. adverse effects.

If we identified substantial heterogeneity, we planned to explore it using subgroup analyses.

Sensitivity analysis

If sufficient numbers of trials were found, we performed sensitivity analyses to test the robustness of the decisions as follows.

1. Repeating meta-analysis after exclusion of studies with inadequate concealment of allocation.
2. Repeating meta-analysis after exclusion of studies in which the outcome evaluation was not blinded.
3. Repeating meta-analysis after imputing missing data as best-possible and worst-possible outcome.
4. Comparing the difference of pooling analysis results by using a fixed-effect model and a random-effects model.

RESULTS

Description of studies

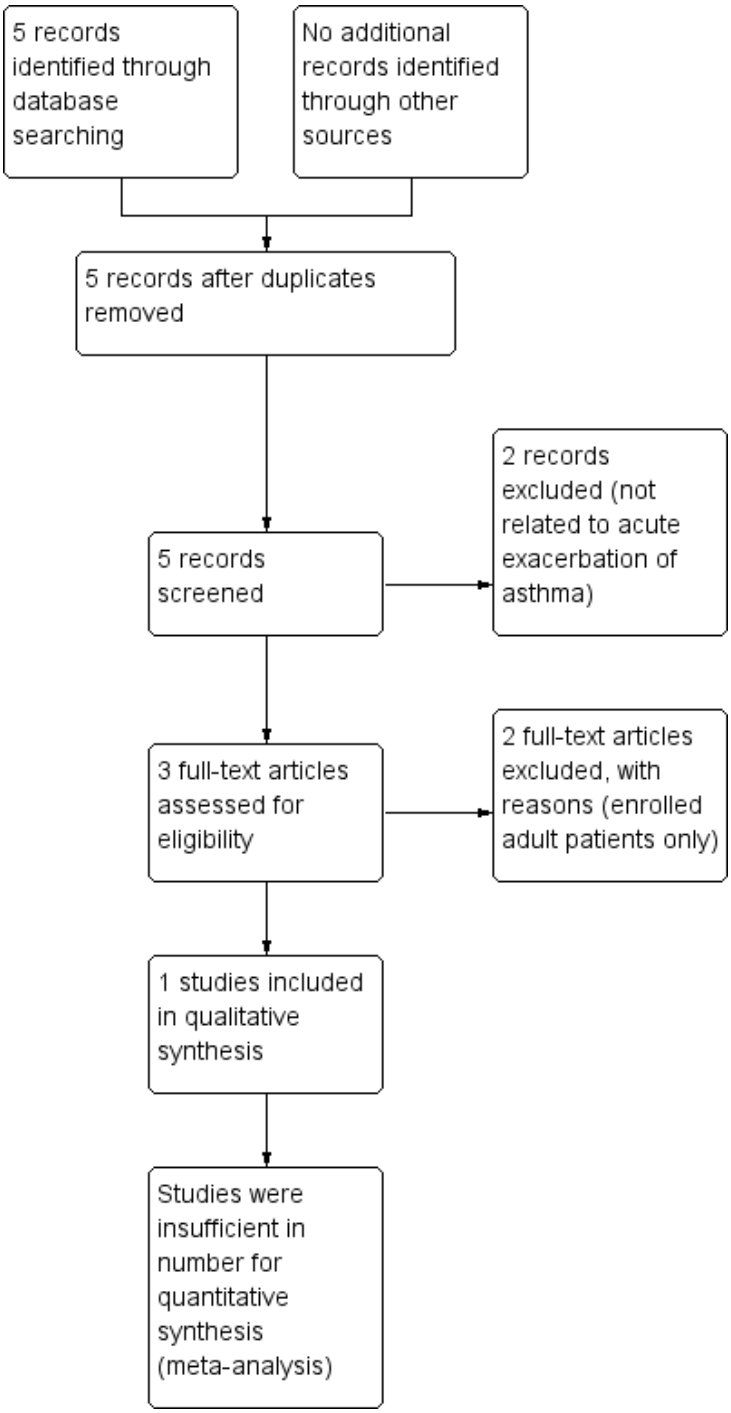
See: Characteristics of included studies; Characteristics of excluded studies.

All the results are based on published data only. We attempted to contact the study authors of the included study by emails to provide missing details, but received no reply.

Results of the search

The electronic searches retrieved five records. No additional records were identified through other sources (Figure 2). All five records were screened for eligibility criteria. Out of these, two trials (not related to acute exacerbation of asthma) were excluded and the remaining three full-text trials were assessed for eligibility. Two full-text trials (enrolled adult patients only) were excluded and the remaining trial was included for qualitative synthesis (Figure 2). There were insufficient trials to allow us to perform a meta-analysis. The latest search was July 2012.

Figure 2. Study flow diagram.



Included studies

One trial (Allen 2005) fulfilled the eligible criteria for the review. Full details of the trial can be found in the Characteristics of included studies table. The included trial was conducted at a paediatric ED of tertiary-care Children's Hospital, Texas, US. This double-blinded, randomised, placebo-controlled trial enrolled 68 children aged two to 18 years (mean age (± SD) 6.1 ± 4.0 years) and presented with acute episode of wheezing. There were 41 males and 27 females. The participants were eligible for enrolment if they had a PIS (Scarfone 2000) of between 8 and 14 after receiving three treatments with nebulised albuterol (2.5 mg/dose or an equivalent six-puff dose of 90 µg/puff) by a metered-dose inhaler with a spacer), nebulised ipratropium bromide (500 µg/dose or an equivalent two-puff dose of 18 µg/dose), and a dose of oral or parenteral glucocorticoids. The eligible subjects were then randomised to receive either ketamine 0.2 mg/kg IV bolus over one to two minutes, followed by a 0.5 mg/kg per hour continuous infusion for two hours or an equivalent volume of normal saline placebo. Thirty-three subjects (mean age (± SD) 5.7 ± 4.3 years; male:female, 21:12) received ketamine and 35 subjects (mean age (± SD) 6.5 ± 3.8 years; male:female, 20:15) received placebo. The enrolment occurred primarily between 7 AM and 11 PM when the primary investigator was available. The ED visits, admissions within the past year because of asthma exacerbations, family history of asthma or atopy, and chronic asthma severity were similar between groups. Primary outcome measure was reduction in PIS and secondary outcome measure was disposition for the enrolled patients after completion of the study.

Excluded studies

Two randomised controlled trials (Hemmingsen 1994; Howton 1996) evaluating ketamine in acute asthma were excluded as both these trials included only adult patients.

Risk of bias in included studies

The risk of bias of included study (Allen 2005) is described in the Characteristics of included studies table and 'Risk of bias' summary (Figure 1).

Allocation

The random sequence was generated using coin flips by the institutional pharmacy.

Blinding

The infusion and bolus were delivered in syringes labelled only with the patient's name and rate of infusion, and their contents were blinded to the nurse, treating physician, investigator and patient. However, it was not stated if contents of the syringes in the two groups were identical in colour or volume. Therefore, it was classified as unclear risk of bias for blinding of participants and personnel.

Incomplete outcome data

Six patients (four in ketamine group and two in placebo group) were removed from the study before completion of two hours of treatment. In the ketamine group, two participants deteriorated requiring additional treatment and intensive care unit (ICU) admission and two participants improved and no longer required continuous albuterol therapy. In the placebo group, one participant deteriorated and one participant improved. The last PIS score at time of removal was carried forwards for analysis by the study authors. The study authors reported no significant difference in results whether they included or excluded these patients from the analysis (Allen 2005).

Selective reporting

Although the study authors reported all the primary (mentioned in materials and methods section of their trial) and secondary (mentioned in results section) outcomes, no study protocol was available and therefore it was considered as unclear risk of bias. We contacted the corresponding study author by email for other outcomes of our review but did not receive a reply.

Other potential sources of bias

The study authors reported no outside funding sources, although conflicts of interest were not mentioned in the published study.

Effects of interventions

Only one study (Allen 2005) enrolling 68 children was eligible for inclusion in the review.

Primary outcomes

No significant differences were reported in respiratory rate and oxygen saturation between the ketamine and placebo groups although no numerical data were provided. No data were available related to PEFR and FEV1. A total of 26 people from the ketamine group (13 in general ward, 10 in intermediate care unit and three

in ICU) and 29 people from the placebo group (18 in general ward, 10 in intermediate care unit and one in ICU) were admitted to hospital. The hospital admission rate was not significantly different between the groups (OR 0.77; 95% CI 0.23 to 2.58). No patients required mechanical ventilation in either group. There were no significant side effects as no patients in either group were removed for dysphoria, laryngospasm, salivation or intolerance of adverse effects. In addition, there were no significant differences in tachycardia and blood pressure reported between the groups (no numerical data were provided).

Secondary outcomes

Two and one child in ketamine and placebo group, respectively, worsened and required other adjuvant therapy. The difference was not significant between the groups (OR 2.19; 95% CI 0.19 to 25.40). Data regarding duration of ED and hospital stay were not available. The authors used PIS as the asthma severity scoring system and the mean decreases in PIS in the ketamine and placebo groups were 3.2 (SD 2.0) and 3.6 (SD 1.3), respectively, and there was no statistically significant difference overall (MD 0.40; 95% CI -1.21 to 0.41) (Allen 2005).

DISCUSSION

Summary of main results

The review evaluated ketamine for management of acute asthma in children. A single study (Allen 2005) with low or unclear risk of bias enrolling 68 non-intubated children demonstrated no significant difference in respiratory rate, oxygen saturation, hospital admission rate and need for mechanical ventilation between the ketamine and placebo groups. The use of ketamine was not associated with significant dysphoria, laryngospasm, salivation or intolerable adverse effects. There was also no difference in need for other adjuvant therapy and in PIS between the groups.

Overall completeness and applicability of evidence

The available evidence was not sufficient to evaluate the efficacy of ketamine for management of acute asthma in children. Based on results of single study, it is difficult to advise for or against the use of ketamine in acute exacerbation of asthma.

Quality of the evidence

The included study (Allen 2005) was reasonably good in methodology as there was low or unclear risk of bias for any of the parameters (Characteristics of included studies).

Potential biases in the review process

We are quite certain that all relevant studies were identified as the search strategy for the review was broad and was performed by the Trials Search Co-ordinator of the Cochrane Airways Group. Two review authors independently performed study selection, data extraction and analysis. There was only one study eligible for inclusion in review. The data for all outcome measures were not available from the published study and there was no reply from the study author when contacted by email.

Agreements and disagreements with other studies or reviews

The included study (Allen 2005) demonstrated that ketamine, given at dose of 0.2 mg/kg followed by an infusion of 0.5 mg/kg per hour for two hours, provided no additional benefit to standard therapy in children with acute asthma exacerbation. In Hemmingsen 1994 (one of the excluded study), 14 mechanically ventilated adult patients with bronchospasm due to any cause (asthma, pneumonia, acute respiratory distress syndrome or sepsis) were randomly allocated to receive either ketamine 1 mg/kg IV or placebo. In people given ketamine, mean PO_2 increased from 10.5 ± 0.5 kPa to 16.4 ± 2.7 kPa ($P < 0.05$), whereas PO_2 in people in the placebo group remained unchanged. The mean PCO_2 remained constant in the ketamine group, but it increased in the placebo group from 5.6 ± 0.9 kPa to 6.1 ± 0.9 kPa ($P < 0.05$). Pulmonary stethoscopic bronchospasm improved immediately after administration of ketamine compared with placebo, although thoracic compliance remained unchanged (Hemmingsen 1994). The second excluded study (Howton 1996) enrolled 53 consecutive patients aged 18 to 65 years with a clinical diagnosis of acute asthmatic exacerbation and a PEFR of less than 40% of the predicted value after three albuterol nebuliser treatments. Patients were randomised to receive either ketamine in a bolus of 0.2 mg/kg followed by IV infusion of 0.5 mg/kg per hour for three hours or a placebo. The bolus dose was lowered to 0.1 mg/kg after the first nine patients because of the occurrence of dysphoric reactions; the infusion dose remained the same. There was no significant difference between ketamine and placebo group in PEFR, respiratory rate, Borg score, FEV1 and hospital admission rate (Howton 1996). Although ketamine had no additional benefit in above two trials (Allen 2005; Howton 1996), it is difficult to form conclusions because participants were different in the studies and in one study (Howton 1996) the bolus dose had to be reduced due to side effects. We found eight case reports and observational studies in the paediatric age group where ketamine was effective

for status asthmatic subjects (Table 1). Out of these, ketamine was used for non-ventilated patients in four studies (Betts 1971; Denmark 2006; Petrillo 2001; Strube 1986) and showed improvement in asthma severity indices and prevented intubation. In the remaining four studies (Fischer 1977; Nehama 1996; Rock 1986; Youssef-Ahmed 1996) ketamine was used for ventilated asthmatic children and there was an improvement in all subjects. There were no significant side effects of ketamine in seven of these studies; however, in Petrillo 2001 ketamine was discontinued prematurely in three out of 10 patients due to adverse effects (one each of hypertension, visual hallucinations and diffuse skin flushing).

Some of these excluded studies appear to show some benefits of ketamine; however, these studies were more prone to bias than randomised controlled trials and as case reports, should be viewed with caution. There might be some possibility that the included trial in this review (Allen 2005) did not show a benefit as the dose of ketamine was lower as compared to some of the other studies in children. However, the case reports in particular are likely to be at risk of bias and do not have the protection that comes from randomisation. The appropriate does of ketamine for acute asthma remains an unanswered question. Another reason for lack of efficacy in the trial may be asthma severity score (PIS), which had some subjective parameters.

AUTHORS' CONCLUSIONS

Implications for practice

The single study on non-intubated children did not show significant benefit and does not support the case studies and observational reports showing benefits of ketamine in both non-ventilated and ventilated children. There were no significant side effects of ketamine in the single, small study included in this review. We could not find any trials on ventilated children.

Implications for research

To prove that ketamine is an effective treatment for acute asthma in children, there is need for a sufficiently powered randomised trial of high methodological quality with objective outcome measures of clinical importance. Future trials should also explore different doses of ketamine and its role in children needing ventilation because of severe acute asthma.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Allen 2005

Methods	Double-blind, randomised, placebo-controlled trial
Participants	68 patients aged 2 to 18 years with acute episode of wheezing who had a PIS of 8 to 14 after receiving 3 treatments with albuterol, ipratropium bromide and their dose of oral or parenteral glucocorticoids
Interventions	Intervention: IV bolus of ketamine at 0.2 mg/kg, followed by a continuous 2-hour parenteral infusion of ketamine at 0.5 mg/kg per hour Placebo: equivalent volume of normal saline
Outcomes	Primary: reduction in PIS score Secondary: disposition for the enrolled patients after completion of the study
Notes	Exclusion criteria: temperature > 39°C (102°F); a focal infiltrate on chest x-ray; use of oral, parenteral or inhaled glucocorticoids within the previous 72 hours; history of prematurity; bronchopulmonary dysplasia; co-existing primary parenchymal pulmonary disease (such as cystic fibrosis) or congenital heart diseases; known hypertension, psychotic disorders, pregnancy and allergy to ketamine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Using a pre-determined randomisation list generated from coin flips by the institutional pharmacy, the patients were then allocated to receive either a 0.2 mg/kg bolus of IV ketamine over 1 to 2 minutes, followed by a 0.5 mg/kg per hour continuous infusion of ketamine for 2 hours, or an equivalent volume of normal-saline placebo as determined by this pre-generated list
Allocation concealment (selection bias)	Low risk	Using a pre-determined randomisation list generated from coin flips by the institutional pharmacy, the patients were then allocated to one of the intervention. The infusion and bolus were delivered in syringes labelled only with the patient's name and rate of infusion, and their contents were blinded to the nurse, treating physician, investigator and patient

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The infusion and bolus were delivered in syringes labelled only with the patient's name and rate of infusion, and their contents were blinded to the nurse, treating physician, investigator and patient. However, authors of the study did not state explicitly that contents of the syringes in 2 groups were identical in colour or volume
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The infusion and bolus were delivered in syringes labelled only with the patient's name and rate of infusion, and their contents were blinded to the nurse, treating physician, investigator and patient
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was done
Selective reporting (reporting bias)	Unclear risk	Although the study authors reported all the primary (mentioned in materials and methods section of their trial) and secondary (mentioned in results section) outcomes, no study protocol was available; therefore it was considered as 'unclear risk of bias'
Other bias	Unclear risk	Conflicts of interest were not mentioned

IV: intravenous; PIS: Pulmonary Index Score.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Hemmingsen 1994	Enrolled only adults (aged 25 to 77 years)
Howton 1996	Enrolled only adults (aged 18 to 65 years)

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Dose comparison of ketamine in included trial and other studies for acute exacerbation of asthma in children

Study ID	Study Type	No. of subjects	Age group	Ketamine dose
Allen 2005 (included trial)	Randomised controlled trial	68	2 to 18 years	0.2 mg/kg IV bolus, followed by a continuous infusion at 0.5 mg/kg/hour for 2 hours
Betts 1971	Case report	1	5 years	4.8 mg/kg IM followed by 0.6 mg/kg IV every 15 minutes for 4 doses
Strube 1986	Case report	1	13 years	1.5 mg/kg IV bolus, followed by infusion at 40 µg/kg/minute (2.4 mg/kg/hour) for 8 hours
Petrillo 2001	Observational study	10	mean 8 (range 5-16) years	IV bolus of 1 mg/kg, followed by infusion at 0.75 mg/kg/hour
Denmark 2006	Case report	2	9 years and 4 years	IV bolus of 2 mg/kg, followed by infusion at 2-3 mg/kg/hour
Fischer 1977	Case report	1	9 years	200 mg IV bolus
Rock 1986	Case report	2		1.0 to 2.5 mg/kg/hour
Nehama 1996	Case report	1	8 months	
Youssef-Ahmed 1996	Retrospective study	17	mean 6 ± 5.7 years	IV bolus of 2 mg/kg, followed by infusion at 32 ± 10 (20-60) µg/kg/minute (1.2-3.6 mg/kg/hour)

IM: intramuscular; IV: intravenous.

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
CENTRAL (*T he Cochrane Library*)	Quarterly (4 issues per year)
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

HISTORY

Protocol first published: Issue 9, 2011

Review first published: Issue 11, 2012

CONTRIBUTIONS OF AUTHORS

Drs. Jat and Chawla conceived the idea for the review. Dr Jat designed and co-ordinated the review. Drs Jat and Chawla performed study selection, data extraction and analysis. Both the review authors approved final version of review.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Asthma [*drug therapy]; Bronchodilator Agents [*therapeutic use]; Disease Progression; Ketamine [*therapeutic use]; Randomized Controlled Trials as Topic; Respiration, Artificial

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant