The Efficacy of Ketamine in Pediatric Emergency Department Patients Who Present With Acute Severe Asthma

Joseph Y. Allen, MD, FAAP  From the Department of Pediatrics, Section of Emergency Medicine, Baylor College of Medicine, Houston, TX.
Charles G. Macias, MD, FAAP

Study objective: We determine whether a continuous infusion of ketamine can decrease the severity of a moderately severe acute asthma exacerbation by a clinically significant 2 points using a 15-point Pulmonary Index scoring scale.

Methods: A double-blinded, randomized, placebo-controlled trial was performed to evaluate patients aged 2 to 18 years who presented to a pediatric emergency department with an acute asthma exacerbation. Exclusion criteria included temperature greater than 39°C (102°F), focal infiltrate on radiograph, or any glucocorticoid use in the last 72 hours. Eligible patients received 3 treatments with albuterol, ipratropium bromide, and a dose of oral or parenteral glucocorticoids. If the Pulmonary Index score remained 8 to 14, enrollment proceeded. All enrolled patients received continuous nebulized albuterol at 10 mg/hour and were randomized to receive an intravenous bolus of 0.2 mg/kg of ketamine, followed by a 2-hour ketamine infusion at 0.5 mg/kg per hour or an equal-volume regimen with normal-saline placebo. A Pulmonary Index score was performed on patients at 0, 30, 60, 90, and 120 minutes.

Results: Sixty-eight patients were enrolled, with 33 randomized to the ketamine infusion and 35 randomized to placebo. Mean ages of patients enrolled, chronic severity of asthma, and duration of symptoms before presentation were similar between groups. At enrollment, the mean Pulmonary Index score in the placebo group was 10.3±1.1 versus 10.5±1.5 for the ketamine group (difference of means 0.2; 95% confidence interval [CI] –0.5 to 0.8). Sixty-two patients completed the entire 2-hour infusion protocol. No significant difference between groups was seen in rate of improvement in the Pulmonary Index score at completion. The mean decrease in the Pulmonary Index scores at the end of the infusion was 3.6±1.3 in the placebo group versus 3.2±2.0 in the ketamine group (difference of means 0.4; 95% CI –0.4 to 1.3). No short-term adverse effects necessitating discontinuation of the infusion or adverse behavioral impacts at 48 hours after discharge were noted.

Conclusion: We conclude that ketamine given at 0.2 mg/kg followed by an infusion of 0.5 mg/kg per hour for 2 hours provided no incremental benefit to standard therapy in this cohort of children with a moderately severe asthma exacerbation. [Ann Emerg Med. 2005;46:43-50.]

INTRODUCTION

Background
Asthma is one of the most common chronic childhood illnesses, affecting 10% of children in the United States.1 Its morbidity and mortality have increased during the last 20 years, and hospitalization rates have doubled for children 1 to 4 years old.1 During this same period, the absolute number of emergency department visits for asthma has increased by 36%, resulting in more than 600,000 visits per year to emergency departments (EDs) by children younger 14 years.2

Children with an acute asthma exacerbation benefit from inhaled albuterol or ipratropium bromide for bronchodilation.3 Oral or parenteral glucocorticoids at a dose of 1 to 2 mg/kg address the inflammatory component and can further reduce admission rates.4,6 Adjunct medicines that have been investigated to reduce bronchoconstriction in children with a severe exacerbation include nebulized dexamethasone,7 intravenous terbutaline,8 and intravenous magnesium sulfate.9,10

Occasionally, a severe asthma exacerbation can progress to respiratory failure, necessitating mechanical ventilation. For these patients, additional bronchodilation can be obtained by using the dissociative anesthetic ketamine for induction. In animal models, ketamine has been shown to induce bronchodilation by several mechanisms: preventing the reuptake...
Editor’s Capsule Summary

What is already known on this topic
Asthma is a common chronic childhood illness, resulting in more than 600,000 emergency department (ED) visits per year for children younger than 14 years.

What question this study addressed
Using a 15-point Pulmonary Index scoring scale to measure improvement, what is the efficacy of ketamine as an addition to standard therapy for pediatric patients who present to the ED with a moderately severe asthma exacerbation?

What this study adds to our knowledge
Thirty-three patients were randomized to ketamine and 35 to placebo. The 2 groups had similar improvement in Pulmonary Index during the study period. Therefore, ketamine, as provided in this study, did not produce any clinically important improvement beyond standard therapy.

How this might change clinical practice
This study provides fairly compelling evidence against the use of this strategy of ketamine administration for asthma unresolved by initial treatment with standard therapy. Study of alternative dosing strategies for ketamine for pediatric patients with asthma may still be warranted.

Importance

The reported efficacy of a ketamine infusion in children has been previously limited to case reports. In 1971, Betts and Parkin14 first reported ketamine being used successfully for bronchodilation of a child with an asthma exacerbation. Huber et al reported measurable bronchodilation in intubated patients using a loading dose of 0.1 mg/lb.11 Sarma later reported avoiding intubation in 2 adults using a ketamine infusion of 0.15 mg/kg per hour,12 whereas Nehama et al15 reported successful bronchodilation of an intubated infant at a rate of 0.2 mg/kg per hour. The range of published successful dosing strategies of ketamine infusions, as well as the patient cohorts who received it, has varied significantly.16-19

One randomized trial by Howton et al20 evaluated ketamine in patients with an acute asthma exacerbation; however, no additional measurable bronchodilation was noted when it was added to standard therapy. Several limitations of the study make it difficult to generalize these results to the pediatric population. The study did not include pediatric patients. Second, the loading dose had to be reduced from 0.2 to 0.1 mg/kg because of dysphoria observed in the first patients who received it. Finally, the scoring scale used required peak flow measurements as markers of improvement, which can be difficult for young children to perform.

Goals of This Investigation

We sought to determine whether an intravenous 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, added to standard therapy for pediatric patients 2 to 18 years of age who presented to an ED with a moderately severe asthma exacerbation could improve symptoms as measured by a previously validated asthma scoring scale.

MATERIALS AND METHODS

Study Design

This study was a randomized, double-blinded, placebo-controlled trial. Written, informed consent was obtained from all patients’ parents or guardians, as well as assent from all patients older than 12 years before enrollment in the study. The study was approved by the Baylor College of Medicine institutional review board for April 2002 until April 2004. Additional approval was required and obtained from the Texas Children’s Hospital Sedation Oversight Committee about the use of ketamine for non-sedation purposes.

Setting and Selection of Patients

Enrollment occurred at a freestanding, urban, tertiary-care, children’s hospital ED from November 2002 through March 2004. Patients aged 2 to 18 years who were triaged as having an acute episode of wheezing were evaluated by a nurse, a respiratory therapist, and a physician (resident, pediatric emergency medicine fellow, or attending physician). The institution uses a reactive airways disease protocol for up to 3 treatments with nebulized albuterol (2.5 mg/dose, with up to 3 nebulized treatments of ipratropium bromide 500 µg/dose). Alternatively, an equivalent 6-puff dose of albuterol (90 µg/puff) by a metered-dose inhaler with a spacer with an equivalent 2-puff dose (18 µg/dose) of ipratropium bromide may be used in the same protocol. During this time, patients also received a 2 mg/kg dose of prednisone or intravenous methylprednisolone (maximum 80 mg). During the study period, there was a nationwide shortage of methylprednisolone. Our institution utilized intravenous dexamethasone 0.4 mg/kg (maximum 15 mg) as the equivalent of methylprednisolone. After 3 treatments, physicians reevaluated the need for additional therapy.

Once the patients received 3 treatments with albuterol, ipratropium bromide, and their dose of oral or parenteral glucocorticoids, the primary investigator used a previously validated 15-point scoring scale called the Pulmonary Index21 to evaluate and score the severity of their asthma exacerbation (Table 1). Previous literature identified scores of 8 or greater as moderate to moderately severe exacerbations.9 If the patients scored from 8 to 14, then enrollment would proceed. To eliminate interobserver variability, only the primary investigator...
evaluated and enrolled patients. Treating physicians or respiratory therapists would attempt to notify the investigator when a patient appeared to require continuous nebulization therapy with albuterol. Enrollment occurred primarily between 7 AM and 11 PM when the primary investigator was available, as well as from 11 PM to 7 AM if the primary investigator was present.

To precisely determine the effect the ketamine infusion would have on reducing acute asthma severity, strict exclusion criteria were established to minimize effects of potential confounders. Patients with temperature greater than 39°C (102°F) or a focal infiltrate on chest radiograph were excluded. Any use of oral, parenteral, or inhaled glucocorticoids within the previous 72 hours precluded enrollment. Patients with a history of prematurity, bronchopulmonary dysplasia, coexisting primary parenchymal pulmonary disease (such as cystic fibrosis) or coexisting congenital heart diseases, known hypertension, psychotic disorders, pregnancy, and allergy to ketamine were also excluded.

**Interventions**

All enrolled patients received nebulized albuterol at 10 mg/hour delivered by an aerosol facemask using 100% oxygen at 8 L/min. Using a predetermined randomization list generated from coin flips by the institutional pharmacy, the patients were then allocated to receive either a 0.2 mg/kg bolus of intravenous ketamine during 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 pregenerated list. The infusion and bolus were delivered in syringes labeled only with the patient’s name and rate of infusion, and their contents were blinded to the nurse, treating physician, investigator, and patient. The patients were observed in the ED during the entire infusion. Additional treatment medications such as ipratropium bromide, magnesium sulfate, and terbutaline were withheld during the 2-hour infusion. A Pulmonary Index score, as well as pulse rate, blood pressure, and oral or axillary temperature, was recorded at 0, 30, 60, 90, and 120 minutes by the primary investigator. Continuous pulse oximetry, cardiac monitoring, and blood pressure monitoring were performed during the entire infusion. Data describing patient characteristics, including age, race, sex, episodes of previous ED visits or inpatient stays for asthma, ICU admissions, the presence of family history of asthma, and duration of symptoms before presentation, were collected on standardized data-collection forms.

Enrolled patients could be removed from the study before completion of the infusion if their status deteriorated and required more aggressive therapy, as determined by the attending physician. The attending physician could also remove the patient if further continuous albuterol therapy was not warranted because of clinical improvement. They could also be removed from the study if adverse effects became intolerable or if the parents wished the study to be discontinued. A final Pulmonary Index score was given at withdrawal, and the reason for withdrawal was recorded.

After the infusion was completed, clinical management was left to the discretion of the attending physician. The patient’s disposition and triage severity of inpatient care setting (when applicable) were tracked. The primary investigator also recorded a guess as to whether the patients received ketamine based on their behaviors during the infusion to assess the impact psychological effects manifested during the infusion had on blinding. Attempts were made to reach all patients by telephone within 48 hours of discharge using a standardized form that inquired about their clinical status and recorded the number of revisits to their primary care provider or ED.

**Primary Data Analysis**

The primary outcome to be assessed was clinical improvement as measured by a clinically significant reduction of the Pulmonary Index score by 2 points, as previously reported by Scarfone et al. In this population of patients with a similar degree of illness at presentation, the SD of the difference was 1.97 points. Setting an α of 0.05 and a power of 80% (β=0.20) resulted in the need to enroll 17 patients per group, for a total of 34 patients who would complete the protocol. We anticipated that 35% to 50% of patients enrolled would not finish the entire 2-hour ketamine infusion. To insure adequate power, we doubled the sample-size enrollment requirements of 68 patients total. Additionally, the increased sample size allowed the detection of a reduced ketamine effect size or a larger SD.

Student’s t tests were used to compare continuous variables between the 2 groups. Repeated measures of analysis of variance were used to assess the effect of time, group allocation, and the interaction between the groups. For patients who did not have all data points available, the last value was brought forward to the missing time points for analysis in an intent-to-treat fashion. Analysis was performed on categoric variables between groups. At the completion of enrollment, an analysis of covariance was performed to examine the interaction of

---

**Table 1. Pulmonary Index.**

<table>
<thead>
<tr>
<th>Score</th>
<th>Respiratory Rate (Breaths/Min)</th>
<th>Wheezing</th>
<th>Inspiratory/Expiratory Ratio</th>
<th>Accessory Muscle Use</th>
<th>Oxygen Saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;6 y</td>
<td>&gt;6 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>&lt;30</td>
<td>&lt;20</td>
<td>None</td>
<td>2:1</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>31-45</td>
<td>21-35</td>
<td>End expiration</td>
<td>1:1</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>46-60</td>
<td>36-50</td>
<td>Entire expiration</td>
<td>1:2</td>
<td>++</td>
</tr>
<tr>
<td>3</td>
<td>&gt;60</td>
<td>&gt;50</td>
<td>Entire breath (none)</td>
<td>1:3</td>
<td>+++</td>
</tr>
</tbody>
</table>

---

"Allen & Macias  Ketamine for Pediatric Patients With Asthma"
patient weight and the efficacy of ketamine in bronchodilation. Analyses were performed on Minitab 11.12 (State College, PA), and Statistical Package for the Social Sciences (SPSS, Inc., Chicago, IL), version 12.0.

RESULTS
The patient-tracking database used in the ED retrospectively identified 694 patients aged 2 to 18 years during the enrollment period who were noted to have the diagnosis of reactive airways disease, wheezing, or status asthmaticus and who were admitted to the hospital from the ED. Of these, 135 patients were listed with a primary or secondary diagnosis of status asthmaticus. A convenience sample of 72 patients who met inclusion criteria was approached for enrollment, with 68 patients consenting to participate. Mean time from administration of glucocorticoids to starting the ketamine infusion was 30 minutes. There were 35 patients in the placebo group and 33 patients in the ketamine infusion group. The mean age for the study cohort was 6.1 ± 4.0 years, with 60% of enrolled being male patients (Figure E1, available at http://www.mosby.com/AnnEmergMed). The intervention and placebo groups were similar with respect to age, sex, and ethnicity, as shown in Table 2. Chronic severity of disease as measured by reported ED visits or in admissions within the past year because of asthma exacerbations, a reported family history of asthma or atopy, and in classification of chronic asthma severity using published guidelines22 were similar between groups as well. Finally, duration of illness between groups before presentation was similar to ensure that neither was potentially more catecholamine depleted. The mean Pulmonary Index scores of the 2 groups were similar at enrollment (10.3 ± 1.1 in the placebo group and 10.5 ± 1.5 in the ketamine group; a difference of means was 0.2; 95% confidence interval [CI] −0.5 to 0.8). These results are summarized in Table 3.

Patient tracking is shown in Figure 1. Five patients were withdrawn after the 90-minute Pulmonary Index score, and 1 was withdrawn after the 60-minute Pulmonary Index score was taken, resulting in 62 patients who completed the infusion. There was no difference in the mean Pulmonary Index score at any interval, nor was there any significant difference in the mean decrease in the Pulmonary Index score during the 2-hour period between the intervention and control groups. Figure 2 graphically shows the mean Pulmonary Index scores for each group at 0, 30, 60, 90, and 120 minutes. At time 120, the Pulmonary Index scores decreased by 3.6 ± 1.3 points in the placebo group and 3.2 ± 2.0 points in the ketamine group (difference of means 1.1; 95% CI 0.4 to 1.8). For the 6 patients who did not have all data points available, the last value collected was brought forward for analysis of variance testing. No differences in the degree of improvement of hypoxia, tachypnea, tachycardia, or blood pressure were noted. A trend was noted in that the heavier children (>35 kg) seemed to receive more bronchodilation.

### Table 2. Patient characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N=35)</th>
<th>Ketamine (N=33)</th>
<th>Difference in Means or Proportions</th>
<th>95% CI for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>6.5 (±3.8)</td>
<td>5.7 (±4.3)</td>
<td>0.8</td>
<td>−1.2 to 2.7</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>20 (57)</td>
<td>21 (64)</td>
<td>7</td>
<td>−14 to 28</td>
</tr>
<tr>
<td>Ethnicity, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>15 (42.9%)</td>
<td>14 (42.4%)</td>
<td>0.5</td>
<td>−19% to 21%</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>16 (45.7%)</td>
<td>13 (39.4%)</td>
<td>6.7</td>
<td>−15% to 29%</td>
</tr>
<tr>
<td>White</td>
<td>3 (8.6%)</td>
<td>3 (9.1%)</td>
<td>0.5</td>
<td>−13% to 14%</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (2.9%)</td>
<td>2 (6.1%)</td>
<td>3.2</td>
<td>−10% to 16%</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (3.0%)</td>
<td>3.0</td>
<td>−8% to 14%</td>
</tr>
</tbody>
</table>

### Table 3. Comparison of asthma severity between groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (N=35)</th>
<th>Ketamine (N=33)</th>
<th>Difference in Means or Proportions</th>
<th>95% CI for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED visits for asthma in previous year</td>
<td>0.8</td>
<td>1.0</td>
<td>−0.2</td>
<td>−0.7 to 0.3</td>
</tr>
<tr>
<td>Previous asthma hospitalizations</td>
<td>0.5 (±0.8)</td>
<td>0.5 (±0.8)</td>
<td>0</td>
<td>−0.4 to 0.4</td>
</tr>
<tr>
<td>Previous ICU admissions for asthma</td>
<td>0.1 (±0.3)</td>
<td>0.03 (±0.2)</td>
<td>0.07</td>
<td>−0.04 to 0.2</td>
</tr>
<tr>
<td>Presence of a family history of asthma/atopy, No. (%)</td>
<td>23 (65.7%)</td>
<td>18 (54.0%)</td>
<td>11.1%</td>
<td>−12% to 34%</td>
</tr>
<tr>
<td>Chronic asthma severity, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild, intermittent</td>
<td>13 (37%)</td>
<td>10 (30%)</td>
<td>7%</td>
<td>−14% to 28%</td>
</tr>
<tr>
<td>Mild, persistent</td>
<td>22 (63%)</td>
<td>22 (67%)</td>
<td>4%</td>
<td>−16% to 24%</td>
</tr>
<tr>
<td>Moderate, persistent</td>
<td>0</td>
<td>1 (3%)</td>
<td>3%</td>
<td>−8% to 14%</td>
</tr>
<tr>
<td>Severe, persistent</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Duration of coughing, hours</td>
<td>14.7</td>
<td>15.7</td>
<td>1</td>
<td>−5.2 to 7.2</td>
</tr>
<tr>
<td>Duration of wheezing, hours</td>
<td>10.9</td>
<td>11.5</td>
<td>0.6</td>
<td>−3.6 to 4.6</td>
</tr>
<tr>
<td>Duration of increased work of breathing, hours</td>
<td>7.1</td>
<td>7.7</td>
<td>0.6</td>
<td>−1.7 to 2.9</td>
</tr>
<tr>
<td>Oxygen saturation at presentation</td>
<td>93.2%</td>
<td>94.1%</td>
<td>−0.9</td>
<td>−2.4 to 0.5</td>
</tr>
<tr>
<td>Pulmonary Index score at enrollment</td>
<td>10.3</td>
<td>10.5</td>
<td>0.2</td>
<td>−0.5 to 0.8</td>
</tr>
</tbody>
</table>
from ketamine because their mean Pulmonary Index scores decreased slightly more than their lighter counterparts during the 2-hour infusion. Figure 3 shows the change in the Pulmonary Index score from time 0 to time 120 by subject. Of the 6 patients who were removed before completion, 2 received the placebo infusion. Magnesium sulfate was used on 1 patient who was later admitted to the ICU and remained hospitalized for 16 days. The other patient in the placebo cohort improved to the degree that continuous albuterol therapy was no longer required, and the patient was subsequently discharged from the ED. The other 4 patients removed before completion were from the ketamine cohort. Two required intravenous terbutaline and increased dosages of nebulized albuterol because of worsening bronchoconstriction. They were admitted to ICU settings, from which they were discharged 3 and 4 days later, respectively. The other 2 patients were removed for improvement and no longer required continuous albuterol therapy. They were later discharged from the ED. No patients in either group were removed for dysphoria, laryngospasm, salivation, or intolerance of adverse effects. No patients in either group required intubation.

A secondary outcome explored was the disposition for the enrolled patients after completion of the study. The patients could be discharged home directly from the ED, admitted to a regular ward, or to higher-triage-level inpatient settings that included the intermediate care and ICUs. Although the study was not powered to detect differences in this secondary outcome, the ketamine and placebo groups were similar in admission rates and higher-triage-level inpatient requirements. Table 4 shows the patient disposition.

For 58 patients, the primary investigator logged a “guess” as to what the patient received and guessed correctly in 37 of the 58 patients (64%; 95% CI 50% to 76%) enrolled. The patient was asked at each scoring interval an age-appropriate query about how they felt. An inquiry of parental perceptions about
the child’s temperament while receiving the infusion was also performed as each point.

Finally, to determine whether ketamine caused any long-term adverse effects, attempts to contact the family by telephone after discharge were made using a standardized questionnaire to assess for the need for a primary care physician or ED revisit within 48 hours after discharge from the hospital. Of the 58 patients who were contacted, 1 patient visited the primary care physician for a scheduled reexamination and needed no subsequent medical intervention. One patient returned to the ED but was treated and discharged. No families reported any nightmares, dysphoria, or long-term abnormal change in behaviors.

LIMITATIONS

There are several limitations to this study. The first is that the bronchodilatory effects of ketamine on patients could not be studied alone. A randomized trial that involved only the use of ketamine without concomitant β agonists in children with asthma would be the best way to isolate and observe their bronchodilatory properties. However, because nebulized β agonists are considered standard therapy for asthma exacerbations, it would be unethical to withhold albuterol in a study design.

A second limitation involved the sensitivity of the scoring scale in detecting changes in improvement. Because a clinically significant improvement has been previously defined and additional patients beyond the required 34 were enrolled who completed the infusion, it is unlikely that the Pulmonary Index score failed to detect these clinical differences as defined a priori. The Pulmonary Index score has components that are subjective, resulting in interobserver variability in measurements. Because young children cannot effectively perform objective measurements of improvements such as peak flow testing, all scales that measure respiratory distress in young children will have inherent subjectivity on clinical characteristics. The fact that the Pulmonary Index score has been previously validated also made it appealing to use.

The use of a single evaluator was selected to eliminate this variability; however, it is important to recognize that this method may reduce generalizability if this investigator assessed children with asthma differently from other physicians. It is unlikely that this differing assessment occurred to a significant extent because the decision to treat patients with continuous albuterol was made by the attending physician and not the investigator, which further suggests that Pulmonary Index scores of greater than 8 given by the primary investigator were appropriate in identifying the cohort of more severely ill children with asthma.
Another limitation of this study is the use of a convenience sample for enrollment that may lead to a sampling bias. With a single investigator enrolling and scoring patients, it was very difficult to evaluate all patients who may have been potential candidates or to perform a detailed comparison of enrolled patients with those who were not. Patients were recruited primarily from 7 AM until 11 PM, with 6 patients being enrolled after 11 PM. This disparity in times of enrollment may create bias if the patient population who had an acute asthma exacerbation during the time when the primary investigator was not available was different from those who presented when he was able to enroll them. Randomization into treatment and placebo groups can reduce some of the bias a convenience sample creates.

There were 6 patients who had the infusion discontinued for improvement or deterioration before the 2-hour completion and did not have all data points collected. It is possible that this subset of patients was different from the rest of the cohort. Analysis of variance testing using the last value brought forward for these 6 patients, as well as excluding them entirely, revealed nearly identical results between the 2 groups. Additionally, all the patients who were removed for improvement went home and all those who were removed for deterioration were admitted to ICU settings in equal ratios in both groups, suggesting that any bias their removal may add is minimal. Two patients in the ketamine cohort and 1 in the placebo cohort received metered-dose inhalers rather than nebulization. These numbers were too small to indicate whether this was of statistical significance, although the clinical impact of receiving metered-dose inhalers rather than nebulizer therapy should be negligible.23 Additionally, when analysis of variance testing was performed, there was no difference in results if they were included or not.

Ketamine has been shown to induce nystagmus and dysphoria that could unblind the primary investigator. With the dosing regimen used in this study, nystagmus was not seen, even though ketamine has known effects on the central nervous system. No patients withdrew because of intolerable adverse effects. The guess as to what the enrolled patient received was correct only 64% of the time, further suggesting that at these doses unblinding was not a significant issue. The limitation that a single investigator performed these evaluations may add bias in this assessment.

**DISCUSSION**

The successful use of ketamine as a continuous infusion for the treatment of children with a severe asthma exacerbation was first reported more than 30 years ago.14 Previously described case series have reported the successful use of ketamine in the management of patients with asthma exacerbations that were recalcitrant to traditional therapies; however, the dosing regimens and severity of patient illness varied significantly because some patients were intubated.11,12,15-19 In contrast, our randomized trial found that ketamine added no additional benefit to standard therapy for nonintubated children with a moderately severe asthma exacerbation, even though our dosing regimen was greater than several of those that reported success.11,12,15

Although it was a negative study outcome, the previously published randomized trial of ketamine for asthma by Howton et al20 was difficult to generalize to children, given its exclusion of patients younger than 18 years and dysphoria that resulted in the lowering of the bolus dose. In choosing our dose, we sought to maximize the risk-benefit ratio of a ketamine infusion in nonintubated children. We thought that dysphoria reported by Howton et al20 with a bolus of 0.2 mg/kg was evidence that a pharmacologic effect of ketamine was occurring. We believed that combining the evidence from their dosing regimen (which was ultimately lower than that in this trial) with the previously described yet limited successful case reports that ultimately resulted in the selection of this dosing regimen would lead to additional measurable bronchodilation while minimizing dysphoria and laryngospasm in children who already were in respiratory distress.

There are several possibilities for a lack of additional measurable effect. The most likely cause is that the dose given was too low for measurable bronchodilation, despite the fact that it was within the ranges described in successful case series. This may reflect the uncertainty of relying on case series for determining clinical efficacy of a therapeutic intervention. Another possibility is that ketamine may be effective only if given in a bolus because its peak effects may fade after 10 to 15 minutes; however, repeated bolus dosing may instead represent an issue of total dose given rather than rate of administration. Finally, it may be that the therapeutic benefit of albuterol at 10 mg/hour is greater than the bronchodilation produced by this ketamine regimen. This effect is more notable in the younger children who received smaller absolute doses of ketamine because analysis of covariance testing revealed that heavier children (>35 kg) seemed to have more bronchodilation attributable to the ketamine infusion. This result may also indicate a relative underdosing of albuterol for the larger patients because all children received nebulized albuterol at 10 mg/hour. Despite this possibility, all enrolled patients were within range of dosing for continuous albuterol therapy, and no published data exist showing that higher-dose albuterol is superior for children with a severe asthma exacerbation.

Because there may be a dose dependency and time effect of ketamine, more rapid infusion and increased dosages may allow a change to be more easily detected with concomitant albuterol administration for patients with a moderately severe asthma exacerbation. However, there may be a limit to the maximum tolerable and ethical doses that can be given to this cohort of awake, nonintubated children. The case series reported by Petrillo et al19 emphasizes the need for clinicians to consider the risk-benefit ratio of using higher doses. Even though it reported successful bronchodilation with its regimen of 1 mg/kg load followed by a 0.75 mg/kg per hour, it unfortunately also resulted in a 40% rate of adverse effects, with 3 of the 10 patients needing the infusion discontinued from therapy prematurely. Additionally, it may be that higher doses of
ketamine in attempts to bronchodilate may oversedate a child and create the false impression of an emergency need for intubation. Therefore, it may be that subsequent studies should focus on the cohort of most severe asthmatic patients for whom intubation appears imminent to more favorably balance the risks and benefits of these higher-dose ketamine infusions.

In Retrospect

Eliminating the exclusionary criteria of the use of inhaled steroids would have allowed more patients to be enrolled. Given that there is a multitude of delivery mechanisms and dosing strategies for the various forms of inhaled glucocorticoids, significant confounders would have been added to determine the effect of ketamine. Multiple enrollers and establishment of interrater reliability could increase enrollment. Creating and validating a scale for asthma with smaller intervals to detect smaller clinically significant differences would be helpful as well.

We conclude that ketamine given at 0.2 mg/kg, followed by an infusion of 0.5 mg/kg per hour for 2 hours, provided no incremental benefit to standard therapy in this cohort of children with a moderately severe asthma exacerbation.

The authors would like to thank the TCH Pharmacy for their assistance with drug preparation; the physicians, respiratory therapists, and nurses who were involved in rapid identification of potential patients; Roland Tadoum, MS, for assistance with histograms; and E. O'Brien Smith, PhD, for statistical analysis.

Supervising editor: David M. Jaffe, MD

Author contributions: JYA and CGM conceived the study, designed the trial, and obtained departmental funding. JYA and CGM supervised the conduct of the trial and data collection. JYA performed all the patient enrollment, data collection, and data entry. JYA and CGM performed all data analysis. JYA drafted the manuscript, and CGM contributed substantially to its revision. JYA and CGM take responsibility for the paper as a whole.

Funding and support: This study was intradepartmentally funded by the Department of Pediatrics, the Section of Emergency Medicine. No outside funding sources were used.


Reprints not available from the authors.

Address for correspondence: Joseph Y. Allen, MD, Texas Children’s Hospital, 6621 Fannin St. MC 1-1481, Houston, TX 77030; 832-824-5497, fax 832-825-5424; E-mail jyallenn@texaschildrenshospital.org.

REFERENCES