The April 2016 Journal Club will be held Wednesday April 27\textsuperscript{th} at Romano’s in Redlands from 6pm to 9pm. Dinner will be provided. Discussion of articles will begin at roughly 6pm. The topic will be:

Non-procedural sedation uses of ketamine

Is ketamine effective in treating pain?
When should we use ketamine to treat asthma?
Is ketamine a safe alternative for treatment of excited delirium?
What is the success rate of ketamine when used for DSI?
Should we use ketamine for refractory status epilepticus in children?
Does ketamine help with preoxygenation in DSI?
Ketamine for depression?
The following individuals have been assigned to present articles (maximum of 5-10 minutes each). Everyone is expected, however, to have reviewed the articles and to be prepared to critically discuss them.

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The Use of Subdissociative-dose Ketamine for Acute Pain in the Emergency Department

Billy Sin, PharmD, Theologia Ternas, PharmD, and Sergey M. Motov, MD

Abstract

Objectives: Ketamine is a well-known anesthetic with its use trailing back to the 1960s. It has antagonistic effects at the N-methyl-D-aspartate receptor. There is emerging literature to suggest the use of subdissociative-dose ketamine (SDDK) for pain reduction. This evidence-based review evaluates the evidence regarding the use of SDDK for acute pain control in the emergency department (ED).

Methods: The MEDLINE and EMBASE databases were searched. Randomized controlled trials (RCTs) that described or evaluated the use of SDDK for acute pain in the ED were included. Literature was excluded if it was not published in English. Duplicate articles, unpublished reports, abstracts, and review articles were also excluded. Quality assessment and evaluation of literature were evaluated based on the GRADE criteria. The primary outcome of interest in this review was the difference in pain score from baseline to cutoff time as specified in the studies. Secondary outcome measures were the incidence of adverse events and reduction in the amount of adjuvant opioids consumed by patients who received SDDK.

Results: Four RCTs met the inclusion criteria, which enrolled a total of 428 patients. Three adult trials and one pediatric trial were identified. The level of evidence for the individual trials ranged from low to moderate. A significant reduction in pain scores was only found in two of the four trials. One trial found a significant reduction in mean pain scores when ketamine was compared to morphine (p < 0.05). Another trial reported a significant decrease in mean distress scores, favoring SDDK over fentanyl (1.0 vs. 2.7, p < 0.05). One trial found a significant reduction in the amount of morphine consumed, favoring ketamine over placebo (0.14 mg/kg, 95% confidence interval [CI] = 0.13 to 0.16 mg/kg vs. 0.2 mg/kg, 95% CI = 0.18 to 0.22 mg/kg; p < 0.001). An emergence phenomenon was reported in one trial.

Conclusions: Four RCTs with methodologic limitations failed to provide convincing evidence to either support or refute the use of SDDK for acute pain control in the ED.


CLINICAL SCENARIO

You are working in the emergency department (ED) and are caring for a 27-year-old female who presents with severe back pain that radiates to her legs. The patient has a past medical history of lumbar radiculopathy. Over the course of 24 hours, her pain has progressively worsened and she is now unable to ambulate due to her pain. Upon physical examination, you find her neurologic functions to be intact. The patient has no known drug allergies. You decide to initiate therapy with 30 mg of intravenous (IV) ketorolac and 5 mg of oral diazepam. Unfortunately, the patient’s pain does not improve. You then decide to order two tablets of acetaminophen 325 mg/oxycodone 5 mg, and trigger point injections with 0.25% bupivacaine. Despite the therapies, the patient’s pain is still not improving. You consult your colleague and a recommendation is made to use subdissociative-dose ketamine (SDDK). Noticing your surprise, he states that patients who present with acute pain may benefit from the therapy. After admitting the patient for intractable lower back pain, you decide to review the evidence to justify the use of SDDK for acute painful conditions in the ED.
INTRODUCTION

The N-methyl-D-aspartate (NMDA) receptor is a ligand-gated channel for the excitatory neurotransmitter glutamate.\textsuperscript{1–5} The stimulation of this receptor has been thought to increase signals and impulses, which lead to hyperalgesic effects.\textsuperscript{1–3} Therefore, it was believed that NMDA antagonists may play a role in pain management. Ketamine is a well-known anesthetic with antagonistic effects at the NMDA receptor. Its role as an analgesic has been well documented in various settings such as cancer or palliative care, perioperative care, and chronic therapy for neuropathic pain.\textsuperscript{6–13} However, the use of ketamine for acute pain is not a common practice in the ED. Its use is often a topic of controversy due its ability to cause adverse events such as dissociation and emergence phenomena.\textsuperscript{2–4,14,15} Recent evidence has emerged that suggests the use of ketamine in subdissociative doses for acute pain control. The objective of this review was to answer the following research question: In ED patients with moderate to severe pain who do not respond to conventional therapies, is the administration of SDDK, compared to placebo, safe and effective in pain control?

METHODS

Criteria for Considering Studies for the Review

Randomized controlled trials (RCTs) that described or evaluated the use of SDDK in the ED were selected for the review.

Participants. Eligible participants included patients of any age range who presented to the ED for acute pain and received at least one dose of SDDK in the ED. Patients who received ketamine in a setting outside the ED or for indications other than analgesia were excluded.

Intervention. The intervention consisted of the administration of SDDK. Subdissociative dose was defined as doses below 1 mg/kg/dose as these were the doses used for the treatment of postoperative or cancer-associated pain in published literature.\textsuperscript{12,13} No restrictions were set for the route of administration.

Comparison. The comparison consisted of the administration of placebo or other pain medications.

Outcomes. The primary outcome of interest in this review was the difference in pain scores from baseline to the cutoff time as specified in the studies. Secondary outcomes included the incidence of adverse events and reduction in the amount of adjuvant opioids consumed by patients who received ketamine.

Search Methods

A search of the MEDLINE database from 1970 to May 2014 and EMBASE from 1970 to May 2014 was conducted. Our search strategies are presented in Data Supplement S1 (available as supporting information in the online version of this paper). Additional references were identified from a review of literature citations. Abstracts were screened for relevance, and publications relating to the use of ketamine as an analgesic for acute pain in the ED were identified. Only literature published in English that evaluated the use of ketamine for acute pain control in humans were included. Duplicate articles, unpublished reports, abstracts, and review articles were not considered. The primary search identified a total of 720 publications. The number of citations was reduced according to their relevance for this review (Figure 1). Eighteen publications were eliminated because they did not meet inclusion criteria. The search identified four RCTs that fulfilled our criteria. We performed our review based on these four publications.\textsuperscript{16–19}

Description of Included Trials

One randomized nonblinded trial and three randomized double-blind trials were identified. All identified trials adhered to the dose range as specified in this section. Analgesic efficacy was measured by the validated scales used in the original studies, and safety was measured by the incidence of adverse events reported in the original studies. In the literature identified, ketamine was used for acute pain control due to fracture reduction, dislocation, burns, abscesses, acute trauma, or generalized pain. Three randomized trials used ketamine as an IV injection with doses ranging from 0.2 to 0.3 mg/kg/dose.\textsuperscript{16–18} One randomized trial utilized ketamine as an IV infusion at 0.1 mg/kg/hr.\textsuperscript{19} The characteristics of the studies included in this review are summarized in Table 1.

Quality Assessment of the Included Studies

Factors that affected study quality, such as randomization, patient selection, adequacy of blinding, and duration of follow-up, were assessed and evaluated based on the GRADE criteria.\textsuperscript{20} Assessment and evaluation were conducted independently by two reviewers (BS, SMM). In the case of discrepancy, a third reviewer (TT) was

Figure 1. The process of selecting studies suitable for inclusion in the final review.
consulted. Subgroup analysis was not possible due to the heterogeneity of the randomized trials. An assessment of the risk and potential biases is summarized in Table 2.

**RESULTS**

A summary of the outcomes from the included literature is presented in Tables 3 and 4.16–19 The data collected from a total of 428 patients revealed conflicting results and conclusions. In two randomized double-blind trials conducted by Messenger et al.16 and Galinski et al.,17 no detectable differences in pain scores were observed. In the trial by Messenger et al., evidence of compromised blinding was reported.16

Gurnani et al.19 conducted a randomized double-blind trial which compared ketamine infusion to intermittent morphine injections for trauma patients. Patients in both groups were provided with morphine 3 mg IV injections if a pain score was ≥5 out of 10 or inadequate analgesia was reported. It was found that patients who received ketamine infusion reported significantly lower pain scores. The trial also reported other findings of interest in patients who received ketamine. First, contrary to other studies, nausea or vomiting were not reported. Second, rescue therapy was not required. In comparison, 18 of 20 (90%) patients in the morphine group required rescue therapy. Finally, there were no reports of hallucinations, disorientation, or oversedation.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparison [Number of Patients Assigned]</th>
<th>Outcome</th>
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<tr>
<td>Messenger et al., 2008</td>
<td>63 patients in a tertiary care hospital</td>
<td>Ketamine 0.3 mg/kg IV [32] vs. fentanyl 1.5 µg/kg IV [31]</td>
<td>Primary: incidence and severity of adverse events Secondary: analgesic adequacy based on 10-point pain scale</td>
<td>Randomized, double-blind controlled trial</td>
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<tr>
<td>Galinski et al., 2007</td>
<td>65 patients in five EDs</td>
<td>Ketamine 0.2 mg/kg IV over 10 minutes and morphine 0.1 mg/kg [33] vs. placebo and morphine 0.1 mg/kg IV [32]</td>
<td>Primary: VAS and opioid consumption at 30 minutes Secondary: patient satisfaction, adverse events</td>
<td>Multicenter, randomized, double-blind trial</td>
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<tr>
<td>Kennedy et al., 1998</td>
<td>260 pediatric patients in a pediatric ED</td>
<td>Midazolam 0.1 mg/kg IV and fentanyl 0.5 µg/kg IV [130] or ketamine 0.5 mg/kg IV [130] every 3 minutes until sedation</td>
<td>Primary: OSBD-R Secondary: parent’s rating of subjects' pain, adverse events, FAS scores</td>
<td>Randomized, nonblinded trial</td>
</tr>
<tr>
<td>Gurnani et al., 2007</td>
<td>40 adult patients in a trauma center</td>
<td>Ketamine 0.25 mg/kg IV followed by IV infusion at 0.1 mg/kg/hr [20] vs. morphine 0.1 mg/kg IV followed by morphine 0.1 mg/kg IV every 4 hours [20]</td>
<td>Primary: VAS, oxygen saturation, demand for adjuvant analgesia, adverse events</td>
<td>Randomized double-blind pilot trial</td>
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FAS = facial affective scale; OSBD-R = Observational Scale of Behavioral Distress–Revised; VAS = visual analogue scale.
One randomized trial evaluated the use of SDDK in the pediatric population. Patients who received ketamine and midazolam were found to have lower distress scores compared to those who received fentanyl and midazolam. A higher incidence of vomiting was found in the ketamine and midazolam group (11 of 130, 8.4%...
vs. 3 of 130, 2.3%; p = 0.03). An emergence phenomenon was reported in one patient. No detectable differences were found in other adverse events.

Despite the use of subdissociative doses, an emergence phenomenon was observed in one pediatric study. Cases of neuropsychological adverse events were reported. However, with the limited data that were provided in the original articles, it was difficult to conclude whether these events were related to dissociation or an emergence phenomenon. All reported adverse events identified in the randomized trials were transient and did not require additional medical intervention, prolonged observation, or hospitalization.

Two studies reported a reduction in the amount of adjuvant opioids consumed by patients who received ketamine. Galinski et al. found that at 30 minutes from baseline, morphine consumption was significantly lower in patients who received ketamine (0.14 mg/kg, 95% confidence interval [CI] = 0.13 to 0.16) compared to placebo (0.20 mg/kg, 95% CI = 0.18 to 0.22; p < 0.05). Gurmani et al. reported a significant reduction in the number of patients who demanded adjuvant morphine, favoring ketamine over placebo (0 of 20, 0% vs. 18 of 20, 90%; p < 0.05). The amount of morphine consumed was not reported by the study authors.

**DISCUSSION**

Returning to the clinical scenario, this review provides some guidance on the use of SDDK in the ED. The review suggests that there is limited evidence to either support or refute the use of SDDK for acute pain control. Ketamine was used as an adjuvant therapy in all randomized trials identified in this review, which had small sample sizes or various methodologic flaws.

There was evidence of unclear documentation or missing records. Data on the use of adjuvant analgesic therapies were lacking. Detailed descriptions of reported adverse events were not available. Various pain scores were used to analyze analgesic effects. CIs that provided information about the point estimates and the degree of uncertainty for the reported pain scores or adverse events were not consistently presented.

In the trial by Messenger et al., patients who received analgesics at ED arrival were required to have a minimum 30-minute washout period. However, the study authors did not present data on the analgesic agents and doses, routes of administration, or times of administration. Thus, it was questionable whether the washout period was sufficient to mitigate potential effects of the analgesics that were administered. Of the trials evaluated in this review, Galinski et al. used the lowest dose of ketamine. It is unclear whether this had an effect on the study results.

Kennedy et al. and Gurmani et al. detected differences in pain scores when ketamine was used as an IV infusion for trauma patients and as an IV injection for pediatric patients. Aside from these two randomized trials, the efficacy of SDDK for pain reduction was also reported in observational studies, case series, a case report, and a survey.

Three observational studies evaluated the use of intranasal ketamine as monotherapy for acute pain. All three studies reported satisfactory pain reduction for most patients within 30 minutes of therapy. Cases of neuropsychological adverse events were reported. Descriptions of neuropsychological events included mood changes, feelings of “unreality,” “spaced out,” “euphoric,” or “disconnected.” Despite these events, the study authors noted that there were no reports of dissociation or emergence phenomenon. In a separate observational study by Sharieff et al., ketamine 15 mg IV was used with propofol for fracture reduction. Of the 20 pediatric patients who were enrolled, one reported a pain score greater than zero, two reported experiencing dreams, and one reported postprocedure vomiting.

In a case series by Lester et al., satisfactory pain control was reported in 19 of 35 (54%) patients who received ketamine as an IV or intramuscular injection. Ketamine was dosed between 0.1 and 0.6 mg/kg/dose. Ineffective analgesia and need for additional opioids were reported in three of 35 (16%) patients. Mild dysphoria was reported in one of 35 (2.8%) patients. Incomplete data were noted in 22.8% of cases.

Richards and Rockford conducted a survey to determine the level of pain reduction, overall satisfaction, adverse events, and patient willingness to receive future treatments with ketamine. Eighteen of 24 patients received ketamine because opioids failed to provide adequate pain relief after 30 minutes. Of the 24 patients who were enrolled, four reported adverse events. Although the description of adverse events was not provided, the authors stated that emergence phenomenon was not reported. Sixteen of 24 patients reported willingness to be treated with ketamine again. Patient satisfaction was reported at 55%, while physician satisfaction was reported at 72%.

An observational study conducted by Ahern et al. further confirmed that therapy with SDDK reduced the amount of opioids required for pain reduction. In this study, ketamine 0.5 mg/kg IV was combined with a reduced dose of hydromorphone. Within 15 minutes of therapy, 20 of the 30 patients reported adequate pain control.

Herring et al. presented a case report which suggested that SDDK may decrease ED length of stay. An adult female presented to the ED with generalized intolerable pain in the head, chest, and back. A review of the patient’s electronic medical records revealed 23 ED visits within a period of 3 years. All visits were for pain-related complaints. The patient’s visits amounted to a total time of 151 hours in the ED. The average ED length of stay was more than 6 hours. In her latest visit, ketamine 15 mg IV injection was administered after lorazepam and morphine failed to provide pain reduction. At 20 minutes postinjection, the patient reported pain relief and was subsequently discharged uneventfully.

Despite various methodologic flaws in the study designs, such as small sample sizes and incomplete descriptions of adverse events or pain scores, the clinical trials identified in this review revealed several promising findings. First, it appears that the use of SDDK may result in satisfactory pain control, and the incidence of adverse events seems to be limited and additional medical intervention is usually not required. Second, SDDK may play a role in reducing the need for...
additional opioids. This may mitigate concerns of opioid overuse in the ED. Finally, most trials reported pain reduction within 5 minutes of initiating therapy. The ability to achieve adequate pain control in a reduced amount of time may lead to a decreased ED length of stay and increased patient satisfaction.

There are other important factors to consider when initiating SDDK in the ED. Clinicians need to determine if ketamine is readily available in the ED. It may be necessary to retrieve ketamine from the central pharmacy if a pharmacy satellite or automated dispensing cabinets are not available. Since it is an anesthetic, hospital policies may require physicians to administer ketamine. IV injections should be administered over 1 minute to prevent respiratory depression. Patients should be periodically monitored for adverse events such as nausea, vomiting, respiratory depression, headache, or disorientation.

LIMITATIONS

This review lacked the qualities of a rigorous systematic review or meta-analysis. Non–English language literature was not evaluated. The quality of the review’s findings was affected by the quality of the original articles. Most of the trials included small sample sizes and used various doses and pain scales to evaluate efficacy. Different patient populations were also evaluated. The CIs were not consistently reported by the original study authors. The combination of these limitations makes it difficult to apply the study findings in a general population.

CONCLUSIONS

This review consisted of four randomized clinical trials enrolling a total of 428 patients. The data failed to provide convincing evidence to either support or refute the use of subdissociative-dose ketamine for management of acute pain in the ED. This review also highlighted the need for well-designed clinical studies to further examine the potential applicability and benefits of subdissociative-dose ketamine. The decision to initiate subdissociative-dose ketamine should be based on assessments of potential risks and benefits of therapy on a case-by-case basis.

References

22. Yeaman F, Oakley E, Meek R, Graudins A. Subdissociative dose intranasal ketamine for limb

Supporting Information
The following supporting information is available in the online version of this paper:
Data Supplement S1. Search strategy for MEDLINE and EMBASE.
Original Contribution

The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED

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Abstract

Objectives: The objective of this study is to describe the clinical use and safety profile of low-dose ketamine (LDK) (0.1-0.3 mg/kg) for pain management in the emergency department (ED).

Methods: This was a retrospective case series of consecutive patients given LDK for pain at a single urban ED between 2012 and 2013. Using a standardized data abstraction form, 2 physicians reviewed patient records to determine demographics, indication, dose, route, disposition, and occurrence of adverse events. Adverse events were categorized as minor (emesis, psychomimetic or dysphoric reaction, and transient hypoxia) and serious (apnea, laryngospasm, hypertensive emergency, and cardiac arrest). Additional parameters measured were heart rate and systolic blood pressure.

Results: Five hundred thirty patients received LDK in the ED over a 2-year period. Indications for LDK were diverse. Median patient age was 41 years, 55% were women, and 63% were discharged. Route of administration was intravenous in 93% and intramuscular in 7%. Most patients (92%) received a dose of 10 to 15 mg. Comorbid diseases included hypertension (26%), psychiatric disorder (12%), obstructive airway disease (11%), and coronary artery disease (4%). There was no significant change in heart rate or systolic blood pressure. Thirty patients (6%) met our criteria for adverse events. Eighteen patients (3.5%) experienced psychomimetic or dysphoric reactions. Seven patients (1.5%) developed transient hypoxia. Five patients (1%) had emesis. There were no cases of serious adverse events. Agreement between abstractors was almost perfect.

Conclusion: Use of LDK as an analgesic in a diverse ED patient population appears to be safe and feasible for the treatment of many types of pain.

1. Introduction

The Institute of Medicine report, Relieving pain in America: a blueprint for transforming prevention, care, education, and research, highlighted inadequate emergency department (ED) treatment of pain as a major public health concern [1]. However, strategies to successfully manage acute pain in a safe and expeditious manner are the source of considerable debate, and there is wide variation in clinical practice [2]. Current pharmacologic strategies in the ED rely heavily on monotherapy with opioids; but adverse events such as sedation, bradypnea, hypotension, and tolerance limit their utility in many patients [3-8]. In addition, the epidemic of opioid pain medication misuse has become a nationally recognized problem, and emergency physicians have been tasked with carefully assessing opioid administration and prescriptions [9]. More than ever, emergency physicians are considering alternative, complimentary medications, such as ketamine, that can be combined with traditional drugs such as opioids and nonsteroidal antiinflammatory drugs, to achieve multimodal analgesia in the acute setting.

Ketamine has been used extensively in the ED for procedural sedation and rapid sequence intubation. An alternative, off-label, use of ketamine is for pain control, using subanesthetic dosing—typically 0.1 to 0.3 mg/kg. Research conducted over the last 15 years has demonstrated that such low-dose ketamine (LDK) is safe, effective, and improves pain management when combined with opioid analgesics [10-13]. Low-dose ketamine has been shown to potentiate the analgesic effect of opioids, have opioid-sparing effects, and to attenuate development of centralized chronic pain states [14-20]. For these reasons, LDK for analgesia has been widely adopted in the anesthesia, surgical, and
palliative care settings for the treatment of postoperative and chronic cancer-related pain.

Emergency medicine has been slower to incorporate LDK for analgesia into routine practice, likely due to lack of familiarity with this indication as well as concerns over adverse effects, particularly emergence phenomena. But a small yet growing body of evidence has emerged over the last 10 years documenting the successful use of LDK in the ED and prehospital environment [12,21-25]. These studies consistently show that the safety and side effect profile of LDK is similar to that of opioids and that LDK causes few significant psychomimetic reactions. In response, some institutions have begun to routinely incorporate LDK into acute pain management as a complimentary and rescue analgesic. Two years ago, in collaboration with emergency physicians, nursing, and pharmacy staff, we developed an ED-specific LDK protocol to facilitate use for a broad array of painful conditions in our department.

The aim of this study is to document the clinical use, safety, and side effect profile of LDK for pain management in the ED.

2. Methods

2.1. Setting

This retrospective, consecutive case series was conducted in a single ED at an urban trauma center. We obtained a database, derived from our electronic medical record (EMR) (Wellsoft Corporation, Sumerset, NJ), of all patients receiving ketamine in our ED during a 2-year period from January 2012 to December 2013. This 2-year timeframe coincided with an increase in popularity and awareness of ketamine on the part of ED providers after the creation of an ED-specific LDK protocol in 2012. With broad inclusion criteria, the protocol proposed LDK as an agent for analgesia in patients with many types of acute or chronic pain, either alone or in combination with additional pain relieving drugs. The protocol recommended doses of 5 to 20 mg intravenous (IV) or 10 to 25 mg intramuscular (IM). There were no absolute contraindications except for known allergy to ketamine. Relative contraindications included age younger than 18 years, uncontrolled seizure activity, severe signs of elevated intracranial pressure, renal and/or liver failure, and women who are pregnant or breastfeeding. Patients were not specifically excluded for having abnormal vital signs (ie, hypertension, tachycardia, or hypoxia), and the ultimate decision whether to order LDK was left up to provider preference.

Our ED uses computerized drug storage units (Pyxis Corporation, San Diego, CA) and EMRs that permit accurate tracking of department drug ordering and administration, including dosage and route of administration. To facilitate ease of use and cut down on unnecessary waste, our pharmacy began stocking preloaded syringes of 15 mg ketamine for IV administration, which were kept in the drug storage units. Our hospital’s institutional review board approved this retrospective review.

2.2. Study population

We extracted data from electronic systems to include all ED patients for whom ketamine was ordered during the study period. The data included medical record number, arrival date, age, sex, disposition, and chief complaint. Chief complaints were categorized into 7 broad groups of indications for LDK before chart review. The groups included musculoskeletal pain, abdominal pain, chest pain, skin and soft tissue infections, headache, back pain, and other. For the purposes of this study, we defined LDK as a dose less than or equal to 20 mg IV or 25 mg IM or roughly 0.1 to 0.3 mg/kg in the average size adult.

2.3. Data abstraction

After a formal training period and data abstraction pilot trial, a standardized data abstraction form was used to review patient records independently by 2 authors. We abstracted ketamine dose (milligram), route of administration (IV or IM) and systolic blood pressure (SBP), and heart rate (HR) at 2 time points: at triage and within 1 hour of LDK administration.

Detailed review of the clinical chart was done to ascertain the presence or absence of specific, predefined adverse events with one hour of LDK administration including cardiac arrest, apnea (respiratory rate <10 breaths per minute or need for jaw thrust and/or bag valve mask ventilation), hypoxia (oxygen saturation, <90% on room air or >5% decreased in oxygen saturation from baseline value if ≥90% at triage), hypertensive emergency (SBP, >180 and the acute onset of chest pain, shortness of breath, or severe headache), laryngospasm, emesis, psychomimetic reaction (agitation, hallucinations, or unusual behavior recorded by provider), and other (nurse or physician documentation of specific problem related to LDK administration).

Frequent meetings were held between abstractors and study coordinators to answer questions, resolve disputes, and review identified adverse events. A random sample of 10% of charts reviewed was duplicated to assess interrater reliability.

2.4. Data analysis

We report descriptive statistics and 95% confidence intervals (CIs), where appropriate. Interrater reliability was ascertained through the Cohen κ statistic for route of administration and absence or presence of any adverse events and the Spearman rank correlation for dose of administration. Statistical analysis was done using Stata version 11 (StataCorp, College Station, TX).

3. Results

We found almost perfect agreement between the 2 abstractors: κ = 0.98 for route of administration, κ = 0.90 for presence of adverse reaction, and τ = 0.99 for dose of administration.

The initial database included 683 patients who received ketamine in our ED over the study period. We excluded all cases of ketamine administration that did not meet our definition of LDK (≥20 mg IV or 25 mg IM). Using this definition, 153 cases were excluded from the analysis. The excluded cases primarily comprised ketamine used for conscious sedation and rapid sequence intubation.

This series ultimately included 530 consecutive ED LDK administrations, of which 294 (55.5%) were female. The median age was 40 years, and the distribution of patients was fairly even between the second to fifth decades of life (Table 1). Indications for LDK were diverse, and many of the patients had substantial underlying illness including hypertension (26%), psychiatric disorder (12%), COPD (11%), and CAD (4%). Ultimately, near two-thirds (63%) were discharged home from the ED.

Low-dose ketamine was administered IV in the vast majority of cases (93%) and IM in the remaining cases. Most patient (92%) received a single dose of either 10 or 15 mg, although the dose range was 5 to 25 mg IV/IM. There was no significant change in SBP and HR within 1 hour of LDK administration, as compared with triage values. Mean triage SBP and HR was 141 (99% CI, 138-144) and 93 (99% CI, 91-95), whereas SBP and HR within 1 hour of LDK administration were 138 (99% CI, 135-141) and 86 (99% CI, 84-88), respectively.

Of 530 LDK cases, only 30 (6%) met our criteria for an adverse event. Each event is specifically detailed in Table 2. There were 7 patients (1.3%)
who developed transient hypoxia, 4 of whom had concurrently received 1 to 2 mg of hydromorphone. Most of the 7 had transient oxygen desaturations to between 86% and 92%, and all but 1 patient responded to 2 L oxygen by nasal cannula. Five patients (1%) had emesis, 3 received ondansetron for symptomatic relief, and all 5 cleared their airway without assistance. There was no evidence of aspiration in any patient.

Eighteen patients (3.5%) experienced psychomimetic or dysphoric reactions (hallucinations, agitation, unusual behavior, or provider documentation of LDK-related patient complaint), none of which were long lasting or led to a change in ultimate disposition. Three patients were given lorazepam for symptomatic anxiety or agitation. Most patients improved without intervention or after reassurance by nurse or physician. There was 1 case of moderate-to-severe agitation in a 57-year-old man with metastatic cancer who was noted by the nurse to open his eyes widely and scream while pulling at the gown she side rails after receiving ketamine 15 mg IV and fentanyl 50 μg IV; he was treated with lorazepam resulting in resolution of his symptoms. Another patient was noted by the nurse to have “a bad dream-like state” and “felt like she might die in her dream,” after receiving ketamine 10 mg IV. Other notable patient quotations in the medical record included, “I feel like a zombie,” “if this is what people feel like on drugs, then I don’t want them,” “my pain is gone, but I feel crazy,” “I feel like I’m flying,” and “you all look like aliens.”

4. Discussion

To our knowledge, this is largest series reported of LDK administration for pain in the ED. We found that LDK is feasible and safe for treatment of a wide variety of painful conditions. The adverse event rate was 6% overall, but the events were easily identified and dealt with by ED staff. Furthermore, this adverse event rate is lower than that of opioid medications in hospitalized patients, although a direct comparison is problematic [26,27]. None of the adverse events caused harm or changed disposition. Importantly, no patients experienced agnepa, laryngospasm, hypertensive emergency, or cardiac arrest.

Concerns over adverse psychomimetic affects, particularly emergence phenomena, have traditionally limited widespread use of LDK in adult ED patients [28]. Our results confirm those of prior smaller studies of LDK showing that psychomimetic reactions are mostly mild in nature and rarely alter a patient’s clinical course [10,12,21–24,29]. In our cohort, 18 patients (3.5%) had documented psychomimetic or dysphoric reactions within 1 hour of LDK administration. Although 3 patients required lorazepam for sedation during the episode, most reactions were mild and improved without intervention or with reassurance from ED staff.

It is now apparent that mild dysphoric effects of LDK occasional occur with doses lower than what is traditionally considered the dissociative range (1–2 mg/kg IV), at which actual emergence phenomenon can occur. The rate of such reactions in recent prospective studies ranges from 16% to 26% [21,22,30]. It is important to note that the negative reactions are universally short lived and differ substantially from emergence phenomenon. Our rate of mild dysphoric events is much lower than described in previous prospective studies; but this is likely due to the inherent limitations of retrospective chart review, reliance on the medical records for documentation of events, and the sensitivity of screening instruments for such events used in prospective studies. Nonetheless, we suspect that some patients reported the effects as negative experiences primarily because they were taken by surprise. Based upon our (the investigators) growing experience with LDK, we believe that advising patients about the possibility of psychomimetic effects reduces the likelihood that the effect will be perceived as negative if it occurs. In addition, a prior prospective trial on LDK showed that the same patient who reports very bothersome dissociative effects might report high satisfaction at discharge [21]. It seems prudent that providers who administer LDK should routinely coach patients just before administration, reassuring them that any dysphoric reaction will be short lived and create as calm an environment as possible.

Other types of adverse events were infrequent. Seven patients (1.5%) experienced transient oxygen desaturation within 1 hour of ketamine administration. Of these patients, 4 were given concomitant opioids with LDK, and all but 1 patient responded quickly with 2 to 4 L nasal cannula oxygen. One patient required 2 hours of bilevel positive airway pressure (bipap) support; but she had been hypoxic at triage, required oxygen support via non-rebreather mask and bipap before LDK, and was already admitted for a COPD exacerbation. According to provider’s documentation, the indication for LDK in this case was to treat chest pain but, perhaps, more importantly, to facilitate therapy for hypoxia by way of providing anxiolysis and bronchodilation. Overall, the rate of hypoxia is substantially less than reported in prior prospective research on opioid-based pain protocols in the ED [31]. For example, in the widely cited “1 + 1” hydromorphone titration protocol study, Chang et al [31] found a 5% rate of hypoxia in patients receiving hydromorphone. In addition, their study excluded patients with baseline oxygen saturation less than 95%. However, a direct comparison with our heterogeneous cohort is not possible because some patients may have been given LDK in spite of their hypoxia.

Similarly, we found a lower rate of emesis in our cohort than what was reported in patients receiving hydromorphone in the study of Chang et al [31] (1% vs 7%, respectively). Furthermore, most of our emesis cases were in patients who had experienced nausea and/or vomiting before receiving LDK (reference, Table 2 for details), whereas such patients would have been excluded from the reporting of emesis in the study of Chang et al [31].

We observed no significant change in blood pressure or HR within 1 hour of administering LDK as compared with triage values. Patients who were tachycardic, hypertensive, or hypoxic at triage remained so after receiving LDK. This is not surprising given the well-established favorable hemodynamic profile of ketamine [32]. Although these findings suggest that LDK may be safe in patients who have abnormal vital signs, there is much uncertainty in this patient population given the limitations of retrospective data. Furthermore, our LDK protocol does not explicitly exclude patients with abnormal vital signs and allows for

### Table 1
Patient characteristics and indications for LDK

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>No. of patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-29</td>
<td>132</td>
<td>25</td>
</tr>
<tr>
<td>30-39</td>
<td>125</td>
<td>24</td>
</tr>
<tr>
<td>40-49</td>
<td>120</td>
<td>22</td>
</tr>
<tr>
<td>50-59</td>
<td>114</td>
<td>22</td>
</tr>
<tr>
<td>60-69</td>
<td>35</td>
<td>6</td>
</tr>
<tr>
<td>&gt;70</td>
<td>4</td>
<td>1</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Sex</th>
<th>No. of patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>236</td>
<td>44</td>
</tr>
<tr>
<td>Female</td>
<td>294</td>
<td>56</td>
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</table>

<table>
<thead>
<tr>
<th>Disposition</th>
<th>No. of patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td>335</td>
<td>63</td>
</tr>
<tr>
<td>Admission</td>
<td>195</td>
<td>37</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indications</th>
<th>No. of patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal pain</td>
<td>63</td>
<td>12</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>178</td>
<td>33</td>
</tr>
<tr>
<td>Chest pain</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Skin and soft tissue infection</td>
<td>62</td>
<td>12</td>
</tr>
<tr>
<td>Back pain</td>
<td>66</td>
<td>12</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Other*</td>
<td>124</td>
<td>23</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>No. of patients</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>139</td>
<td>26</td>
</tr>
<tr>
<td>CAD</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>COPD</td>
<td>57</td>
<td>11</td>
</tr>
<tr>
<td>Psychiatric illness b</td>
<td>63</td>
<td>12</td>
</tr>
</tbody>
</table>

* Included chronic pain, sickle cell crisis, genitourinary disorders, painful rashes, psychiatric complaints, and other miscellaneous painful complaints.

b Includes depression, bipolar disorder, and schizophrenia.

[26,27]
<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Age</th>
<th>Sex</th>
<th>Disposition</th>
<th>Indication</th>
<th>Dose</th>
<th>Route</th>
<th>Comorbidities</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia⁷</td>
<td>41</td>
<td>F</td>
<td>Home</td>
<td>Abdominal pain</td>
<td>15</td>
<td>IV</td>
<td></td>
<td>LDK given for chronic pelvic pain. Hypoxia noted during LDK administration requiring non-rebreather facemask, which resolved within 1 h. Patient had been given 2 mg hydromorphone 45 minutes before LDK.</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>M</td>
<td>Admit</td>
<td>Abdominal pain</td>
<td>10</td>
<td>IV</td>
<td>Depression, hypertension</td>
<td>LDK given for abdominal pain. Placed on 2-L nasal cannula after LDK, although no desaturation was noted.</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>M</td>
<td>Admit</td>
<td>Abdominal pain</td>
<td>15</td>
<td>IV</td>
<td>Hypertension, CAD</td>
<td>LDK given for abdominal pain secondary to diabetic ketoacidosis. 45 min prior received 2 mg hydromorphone. SpO₂ dropped to 88%, transient 2-L NC applied.</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>M</td>
<td>Admit</td>
<td>Abscess</td>
<td>20</td>
<td>IV</td>
<td></td>
<td>LDK given for abscess drainage. 1 h after administration noted to have SpO₂ of 88% when asleep, which improved with elevation head of bed.</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>M</td>
<td>Home</td>
<td>Cancer</td>
<td>15</td>
<td>IV</td>
<td>Hypertension, COPD</td>
<td>Patient may have had undiagnosed obstructive sleep apnea.</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>F</td>
<td>Admit</td>
<td>COPD</td>
<td>15</td>
<td>IV</td>
<td>Hypertension, COPD</td>
<td>Patient was admitted for COPD. SpO₂ 95% on 2-L NC before LDK but dropped to 80% with increased work of breathing and lethargy obstructive lung disease noted by MD afterward. Placed on bipap for next 2 h then improved.</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>M</td>
<td>Admit</td>
<td>Trauma</td>
<td>20</td>
<td>IV</td>
<td></td>
<td>LDK and 1 mg hydromorphone given for head laceration repair. SpO₂ dropped to 90%, transient 2-L NC applied.</td>
</tr>
<tr>
<td>Emesis</td>
<td>21</td>
<td>M</td>
<td>Admit</td>
<td>Abdominal pain</td>
<td>15</td>
<td>IV</td>
<td></td>
<td>LDK and 8 mg ondansetron given for nausea and vomiting in setting of pylonephritis. Patient had 2 small episodes of emesis afterward but stated “it’s due to not eating.”</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>F</td>
<td>Home</td>
<td>Abdominal pain</td>
<td>15</td>
<td>IV</td>
<td>Hypertension</td>
<td>LDK, 25 mg benedryl and 4 mg ondansetron given for nausea and vomiting in setting of gastroparesis. Patient had large emesis 45 min afterward, improved with 10 mg metoclopramide.</td>
</tr>
<tr>
<td></td>
<td>51</td>
<td>M</td>
<td>Home</td>
<td>Back pain</td>
<td>15</td>
<td>IV</td>
<td>Hypertension</td>
<td>LDK, 30 mg ketorolac and 10 mg dexamethasone given for cauda equina syndrome. Patient had small emesis 15 min afterward while lying flat for electrocardiogram.</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>F</td>
<td>Home</td>
<td>Chronic pain</td>
<td>15</td>
<td>IV</td>
<td></td>
<td>LDK given for chronic abdominal pain and hyperemesis syndrome. Patient complained of continued nausea and vomiting after LDK.</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>F</td>
<td>Home</td>
<td>Fracture</td>
<td>15</td>
<td>IV</td>
<td>Hypertension</td>
<td>LDK and 1 mg hydromorphone given for humerus fracture. Patient had large emesis 10 min afterward, improved with 4 mg ondansetron.</td>
</tr>
<tr>
<td>Psychomimetic/dysphoric⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>M</td>
<td>Home</td>
<td>Abdominal pain</td>
<td>10</td>
<td>IV</td>
<td></td>
<td>After LDK and 2 mg hydromorphone, patient reported, “I feel dizzy.”</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>F</td>
<td>Home</td>
<td>Abdominal pain</td>
<td>5</td>
<td>IV</td>
<td></td>
<td>After LDK and 400 mg ibuprofen, patient reported, “I feel dizzy.”</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>F</td>
<td>Home</td>
<td>Abdominal pain</td>
<td>15</td>
<td>IV</td>
<td>COPD</td>
<td>After LDK and 1 mg hydromorphone, patient stated her pain is improved, but the medicine made her feel “like I’m going to die.”</td>
</tr>
<tr>
<td></td>
<td>67</td>
<td>F</td>
<td>Home</td>
<td>Abdominal pain</td>
<td>15</td>
<td>IV</td>
<td>Hypertension</td>
<td>After LDK, noted that she does not want ketamine again for pain; that it made her hallucinate.</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>F</td>
<td>Home</td>
<td>Abdominal pain</td>
<td>15</td>
<td>IV</td>
<td>CAD, COPD</td>
<td>After LDK and 4 mg morphine, patient reported “pain gone” but “I feel crazy.” Given 1 mg lorazepam.</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>F</td>
<td>Home</td>
<td>Abdominal pain</td>
<td>15</td>
<td>IV</td>
<td></td>
<td>After LDK and 4 mg morphine, patient noted to have enlarged eyes and be screaming in pain while pulling at side rails. Required 2 mg lorazepam and was calmed by MD</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>F</td>
<td>Admit</td>
<td>Abdominal pain</td>
<td>20</td>
<td>IV</td>
<td></td>
<td>After LDK, patient reported “I feel dizzy, but the pain is gone.” Later noted by RN to patting the wall with hand repeatedly with eyes closed. She remained alert and oriented but no explanation offered.</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>F</td>
<td>Admit</td>
<td>Abscess</td>
<td>10</td>
<td>IV</td>
<td></td>
<td>LDK and 25 μg fentanyl given for abscess drainage. Noted to become anxious and was crying because she “didn’t like the effect of the drug.”</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>F</td>
<td>Home</td>
<td>Back pain</td>
<td>10</td>
<td>IV</td>
<td>Hypertension</td>
<td>LDK and 2 mg hydromorphone given for back pain. Noted to be very anxious for 10 min afterward.</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>F</td>
<td>Home</td>
<td>Back pain</td>
<td>15</td>
<td>IV</td>
<td></td>
<td>After LDK, patient became highly anxious and was crying. Reported “I feel like a zombie.” Improved with reassurance by nurse.</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>M</td>
<td>Admit</td>
<td>Cancer</td>
<td>15</td>
<td>IV</td>
<td></td>
<td>After LDK and 50 μg fentanyl, patient noted to have enlarged eyes and be screaming in pain while pulling at side rails. Required 2 mg lorazepam and was calmed by MD</td>
</tr>
<tr>
<td></td>
<td>65</td>
<td>F</td>
<td>Admit</td>
<td>Chest pain</td>
<td>15</td>
<td>IV</td>
<td>COPD</td>
<td>After LDK, noted to be anxious and disoriented by nurse. Patient stated “If this is what people feel like on drugs, then I don’t want them.” Feelings resolved spontaneously within 10 min.</td>
</tr>
<tr>
<td></td>
<td>67</td>
<td>F</td>
<td>Admit</td>
<td>Chest pain</td>
<td>15</td>
<td>IV</td>
<td>Hypertension, coronary</td>
<td>Patient did not like feeling of LDK immediately, and the bolus was stopped before completion.</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>M</td>
<td>Home</td>
<td>Chest pain</td>
<td>15</td>
<td>IV</td>
<td>Hypertension</td>
<td>Received LDK for asthma exacerbation. Afterward, noted to be more calm and stated “I feel like I’m flying,” then “I’m going to sleep.”</td>
</tr>
<tr>
<td></td>
<td>38</td>
<td>F</td>
<td>Home</td>
<td>Chest pain</td>
<td>10</td>
<td>IV</td>
<td></td>
<td>During LDK administration, noted to have “a bad dream-like state,” and “felt like she was going to die in her dream.”</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>F</td>
<td>Home</td>
<td>Chest pain</td>
<td>15</td>
<td>IV</td>
<td>Hypertension</td>
<td>After LDK noted, “I feel weird. I feel funny…What is wrong with me?” Symptoms resolved without intervention.</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>M</td>
<td>Home</td>
<td>Hematoma</td>
<td>15</td>
<td>IV</td>
<td></td>
<td>After LDK and 1 mg hydromorphone, patient reported pain is gone, but “we all look like aliens.”</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>F</td>
<td>Home</td>
<td>Sickle cell pain</td>
<td>15</td>
<td>IV</td>
<td>Depression, hypertension</td>
<td>After LDK, patient became nauseated and flushed feeling. Improved with 25 mg phenergan.</td>
</tr>
</tbody>
</table>

Abbreviations: M, male; F, female; SpO₂, oxygen saturation as measured by pulse oximetry; NC, nasal cannula; MD, doctor of medicine; RN, registered nurse. ⁷ No patient experienced cardiac arrest, apnea, hypertensive emergency, or laryngospasm. ⁸ Significant comorbidities abstracted included history of hypertension, psychiatric illness (depression, bipolar, and schizophrenia), CAD, and COPD. ⁹ Hypoxia was defined as oxygen saturation as measured by pulse oximetry less than 90% or decrease in oxygen saturation more than 5% from triage vital signs. ⁴ Psychomimetic/dysphoric side effects were defined as hallucinations, agitation, unusual behavior, or registered nurse/doctor of medicine documentation of a specific problem related to ketamine.
provider preference, so we cannot account for individual practice patterns and must assume some avoided LDK in these situations.

The favorable safety profile of LDK is especially notable given the wide age distribution and prevalence of comorbidities in our cohort (Table 1). To date, prior studies of LDK had rigorous inclusion and exclusion criteria and represented a tightly controlled cohort of patients. We believe that our cohort represents a typical diverse, urban ED population, where many patients have chronic medical and psychiatric disease, substance abuse, and lack of social support. In spite of this, our findings are consistent with those of a prior small retrospective study in a similar setting [25] and recent prospective data [21,22,24,30], showing that LDK is feasible, generally well tolerated, and very safe in the ED.

This study has the usual limitations inherent in a retrospective review. Quality of the data was dependent on that of the medical record, particularly nursing documentation. To mitigate this, we focused on data that were objective and not prone to interpretation or abstraction bias using a standardized abstraction protocol based upon accepted guidelines for chart review methodology [33]. Our EMRs include extensive documentation from nursing and physicians, so it is unlikely that we missed any major adverse events (ie, cardiac arrest, apnea, hypoxia, laryngospasm, and hypertensive emergency). Despite this, it is likely we underestimated minor adverse events, such as emesis or transient psychomimetic and dysphoric events.

Although emergency physicians should be encouraged by the safety of LDK in this large and diverse cohort of ED patients, we emphasize that data from prospective, randomized blinded trials are needed to definitively determine the efficacy, safety, and side effect profile of LDK compared with standard opioid analgesics and other opioid adjuncts.

5. Conclusion

Use of LDK alone or in combination with other pain medications as a primary or rescue analgesic in a diverse ED patient population appears to be safe and feasible for the treatment of many types of pain. Minor psychomimetic side effects were observed but easily addressed by ED personnel and did not alter disposition. Other side effects, including emesis and hypoxia, appear to be equally or less common than reported with opioids. Prospective randomized trials are needed to determine the efficacy and further elucidate the safety and side effect profile of LDK.

References


Low-dose ketamine vs morphine for acute pain in the ED: a randomized controlled trial

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c Department of Emergency Medicine, Bayne-Jones Army Community Hospital, Fort Polk, LA
d Air Force En Route Care Research Center, San Antonio Military Medical Center, Houston, TX

Abstract

Objectives: To compare the maximum change in numeric rating scale (NRS) pain scores, in patients receiving low-dose ketamine (LDK) or morphine (MOR) for acute pain in the emergency department.

Methods: We performed an institutional review board–approved, randomized, prospective, double-blinded trial at a tertiary, level 1 trauma center. A convenience sample of patients aged 18 to 59 years with acute abdominal, flank, low back, or extremity pain were enrolled. Subjects were consented and randomized to intravenous LDK (0.3 mg/kg) or intravenous MOR (0.1 mg/kg). Our primary outcome was the maximum change in NRS scores. A sample size of 20 subjects per group was calculated based on an 80% power to detect a 2-point change in NRS scores between treatment groups with estimated SDs of 2 and an α of .05, using a repeated-measures linear model.

Results: Forty-five subjects were enrolled (MOR 21, LDK 24). Demographic variables and baseline NRS scores (7.1 vs 7.1) were similar. Ketamine was not superior to MOR in the maximum change of NRS pain scores, MOR = 5 (confidence interval, 6.6–3.5) and LDK = 4.9 (confidence interval, 5.8–4). The time to achieve maximum reduction in NRS pain scores was at 5 minutes for LDK and 100 minutes for MOR. Vital signs, adverse events, provider, and nurse satisfaction scores were similar between groups.

Conclusion: Low-dose ketamine did not produce a greater reduction in NRS pain scores compared with MOR for acute pain in the emergency department. However, LDK induced a significant analgesic effect within 5 minutes and provided a moderate reduction in pain for 2 hours.

1. Introduction

Pain is the most common complaint for emergency department (ED) visits [1]. Opioids, commonly morphine, are the standard treatment of moderate and severe, acute pain in the ED. However, many patients report inadequate pain control in the ED [2,3]. Patients with opioid dependence may present to the ED in anticipation of obtaining treatment with opioids [4]. In addition, the serious adverse effect profile of opioids can be underestimated given their common use in the ED. In 2012, the Joint Commission released a Sentinel Event Alert, which stated that opioid analgesics rank among the drugs most frequently associated with adverse drug events. Of the opioid-related adverse drug events—including deaths—that occurred in hospitals and were reported to The Joint Commission’s Sentinel Event database (2004–2011), 47% were wrong dose medication errors, 29% were related to improper monitoring of the patient, and 11% were related to other factors, including excessive dosing, medication interactions, and adverse drug reactions [5].

Like opioids, ketamine has analgesic properties [6–9]. Ketamine, however, has a very large therapeutic window. Overdoses from 5 to 100 times the therapeutic dose have been reported without adverse outcomes [10]. In addition, the adverse effect profile of ketamine (elevated pulse and blood pressure, hallucinations, emergence) is much different from that of opioids (decreased pulse, blood pressure, and respiratory rate, sedation).

The predominant use of ketamine in the ED, as well as the focus of research, has been as a dissociative agent (1.5–2 mg/kg intravenous [IV]) to facilitate procedural sedation [11–14]. There were a small number of non-ED studies with low-dose ketamine (<0.55 mg/kg IV) from as early as the 1970s which reported efficacious analgesia without dissociation [15,16]. More recent studies from the ED and prehospital environment have shown that low-dose ketamine, when used alone or in combination, provides safe and efficacious analgesia [8,9,17–19]. These studies, however, are limited in that opioids or sedatives were used in conjunction with low-dose ketamine; patients were treated for chronic pain, not acute pain, or there was no comparison arm.

* Grant: We received a research grant from the Office of the Air Force Surgeon General to support this study (Award No. C.2011.173).
☆☆☆ Meetings: Society for Academic Emergency Medicine Annual Meeting; Atlanta, GA; May 2013; oral presentation.
Studies are needed to independently compare the safety and efficacy of opioids to other analgesics, such as ketamine, in order to ensure that patients are receiving the safest and most effective pain management possible when experiencing acute pain in the ED. Thus far, a prospective, randomized, double-blinded trial comparing low-dose ketamine alone to morphine for the treatment of acute pain in the ED has not been reported.

The goal of this study was to compare the ability of low-dose ketamine and morphine to reduce acute pain as measured by the numeric rating scale (NRS). In addition, we describe the details of ketamine analgesia over time in an ED population. Finally, we also sought to examine the reduction of pain as measured by provider and nurse satisfaction scores.

2. Methods

2.1. Study design

Our study was a prospective, randomized, controlled, double-blinded, superiority trial comparing the efficacy of IV low-dose ketamine to IV morphine for moderate to severe acute pain in the ED setting. We hypothesized that ketamine would provide a greater maximum reduction in pain compared with morphine. The Brooke Army Medical Center Institutional Review Board in San Antonio, TX, approved the study protocol. Written and signed informed consent was obtained in accordance with institutional policy.

2.2. Setting

The study was conducted in a military, level 1 trauma center ED, where approximately 80,000 ED patients are treated annually. The ED patient population consists of uniformed military personnel (20%) and civilians (80%). Enrollment occurred from February 2012 to March 2013.

2.3. Study protocol

A convenience sample of patients was obtained by a full-time, trained, research nurse coordinator using a standard enrollment protocol. Patients were screened at triage during daytime and evening hours on weekdays. Patients were eligible for inclusion if they were between the ages of 18 and 59 years and complained of abdominal, flank, low back, or extremity pain that the ED provider felt warranted IV opioid treatment. Patients were excluded if any of the following were met: oxygen saturation less than 95%, systolic blood pressure less than 90 mm Hg or greater than 180 mm Hg, pulse rate less than 50 or greater than 120 beats/min, altered mental status, intoxication, fibromyalgia or other chronic pain condition requiring the use of opioids or tramadol as an outpatient, ischemic heart disease, heart failure or unstable dysrhythmias, use of an opioid or tramadol within 4 hours prior to enrollment, an allergy to morphine or ketamine, required pain medication immediately after triage and the blinded study protocol. The Brooke Army Medical Center Institutional Review Board in San Antonio, TX, approved the study protocol. Written and signed informed consent was obtained in accordance with institutional policy.

Eligible patients, in whom opioid analgesia was anticipated, gave written consent immediately after triage and the blinded study protocol was implemented: (1) if the provider prescribed opioid analgesia and (2) if the provider was agreeable after being made aware of the patient’s consent to the protocol. The trial was open to all patients regardless of the provider and nurse caring for the patient. All enrolled patients gave written consent.

Once enrolled, patients were assigned a random study identification number and an opaque envelope. The envelopes were prepared by the research team and contained the study drug and dose. Upon enrollment, the research nurse would obtain the assigned opaque envelope and give it to a trained clinical nursing specialist (CNS). The CNS would then open the envelope containing a presigned prescription with the assigned medication and weight-based dosing. The CNS would obtain the drug from the ED dispensing system in an unlabeled syringe, dilute the medication to 10 mL (a 20-mL syringe was used if the body weight precluded the medication from fitting into a 10-mL syringe) using normal saline as indicated, and infuse the medication for 5 minutes. Unused medications were disposed of using standard nursing protocols.

An initial dose of ketamine at 0.3 mg/kg of total body weight (maximum dose 25 mg) was infused intravenously for 5 minutes, or morphine at 0.1 mg/kg of total body weight (maximum dose 8 mg) was infused intravenously for 5 minutes. Completion of the initial infusion was considered time zero. A second dose could be given as early as 20 minutes after completion of the initial dose and was the same dose as the first dose. The protocol allowed for midazolam treatment of agitation or emergence reactions and naloxone treatment of evidence of opioid overdose. All other medication reactions were treated at the provider’s discretion. If the patient requested a third dose of pain medication, data collection stopped, the provider was notified, and the patient was eligible for open-label pain medication of the providers choosing (Fig. 1).

There was one major protocol deviation. The CNS calculated the dose of the study medication based on the patient’s weight and administered the weight-based dose to the patient. The resulting dose was greater than the maximum dose allowed by the protocol. There were no adverse events as a result of this deviation, and the deviation was reported to our institutional review board.

Patients who met inclusion/exclusion criteria were consented for the study by a research nurse. N = 45

If the treating physician prescribed IV opioids the research nurse informed the treating physician that the patient had consented to the study. N = 45

If the treating physician approved of the patient’s enrollment the patients were randomly assigned to the MOR or LDK group. N = 45

The patient received and initial dose of the study drug. After 20 minutes the patient was asked if another dose of the study drug was needed. This question was repeated every 20 minutes until a total of 120 minutes had elapsed. If the patient requested a 3rd dose of medication, underwent procedural sedation, was discharged from the ED or asked to withdraw, the protocol was stopped. N = 45

Fig. 1. CONSORT diagram. SAMMC, San Antonio Military Medical Center; MOR, morphine; LDK, low-dose ketamine.
2.4. Measures

Our primary outcome measurement was the maximum change on the verbal NRS pain scale compared with their initial score (baseline). The NRS was used to measure a patient’s subjective level of pain on a scale from 0 (representing no pain at all) to 10 (the worst pain imaginable) using whole numbers. This scoring system is commonly used in the ED and correlates well with the visual analog scale [20] and has been used in clinical trials [20–24]. The NRS score was documented just prior to the administration of the study drug (time zero). After infusion of the study drug was complete, NRS scores were documented at 5, 10, 20, and then every 20 minutes thereafter up to 120 minutes. We stopped recording NRS scores prior to 120 minutes if the patient was discharged from the ED, underwent procedural sedation, or requested a third dose of the study drug.

The secondary outcomes included levels of agitation or sedation measured by the Richmond Agitation-Sedation Scale (RASS), vital signs, adverse events, and the need for repeating dosing [25,26]. Providers and nurses were surveyed after the patient encountered end to rate their satisfaction with the study medication. They scored the medication as “very dissatisfied” (1), “somewhat dissatisfied” (2), “neither satisfied nor dissatisfied” (3), “somewhat satisfied” (4), or “very satisfied” (5).

All data were collected by our research nurse and stored in a locked, password encrypted, electronic database (Microsoft Excel, v14; Microsoft, Redmond, WA).

2.5. Data analysis

Power analysis determined that a sample size of at least 20 subjects per group would achieve 80% power to detect a 2-point change in NRS scores between treatment groups, with estimated group SDs of 2 for a 2-sided test with a significance level \( \alpha \) of .05 (PASS-NCCS, 2011, Kaysville, UT). We used a repeated-measures linear model with adjustments for treatment group, time, and the group by time interaction with an autoregressive covariance structure (SAS Version 9.3 for Windows; SAS Institute, Cary, NC). Differences between drug groups were tested using a signi

The primary outcome measurement was the maximum reduction in NRS score from baseline between the 2 groups (Table 2). The maximum change in NRS pain score, from baseline, in the low-dose ketamine group was 4.9 (95% confidence interval [CI], 5.8–4.4). The maximum change in NRS pain score, from baseline, in the morphine group was 5 (95% CI, 6.6–3.5). The maximum change in NRS pain score took place at 5 minutes (T5) in the low-dose ketamine group and at 100 minutes (T100) in the morphine group.

We reported the NRS scores as a percentage change from baseline over time. In the morphine group, there was a steady trend of reduced pain over time. In the ketamine group, there was an initial decrease in pain scores followed by a rapid increase in pain scores within the first 20 minutes. However, after the 20-minute mark, the pain decreased by greater than 50% from baseline in the low-dose ketamine group (Fig. 2).

A second dose was administered in 38% of the morphine group vs 54% of the ketamine group (Table 4). No differences were found in diastolic blood pressure, heart rate, respiratory rate, or oxygen saturations (Figs. 5–8). No differences were found in diastolic blood pressure, heart rate, respiratory rate, or oxygen saturations (Figs. 5–8).

Fourteen patients (58%) in the low-dose ketamine group and 12 (57%) patients in the morphine group described adverse effects (Table 4). One patient in the morphine arm had a transient oxygen desaturation to 88%, which resolved after 5 minutes of oxygen via nasal cannula at 4 L/min. Two patients in the morphine and 3 patients in the ketamine arm were treated for nausea. One patient in each group

### Table 1

<table>
<thead>
<tr>
<th>Patient characteristics by treatment group</th>
<th>Morphine</th>
<th>Low-dose ketamine</th>
<th>Both treatment groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean (SD)</td>
<td>29 (10)</td>
<td>31 (12)</td>
<td>30 (11)</td>
</tr>
<tr>
<td>Male sex</td>
<td>9 (43)</td>
<td>14 (58)</td>
<td>23 (51)</td>
</tr>
<tr>
<td>Vital signs, mean (SD)</td>
<td>121 (11)</td>
<td>126 (14)</td>
<td>124 (13)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>74 (11)</td>
<td>76 (11)</td>
<td>75 (11)</td>
</tr>
<tr>
<td>Pulse rate (BPM)</td>
<td>18 (3)</td>
<td>18 (3)</td>
<td>18 (3)</td>
</tr>
<tr>
<td>Respiratory rate (RPM)</td>
<td>98 (1)</td>
<td>98 (2)</td>
<td>98 (2)</td>
</tr>
<tr>
<td>Oxygen saturations (%)</td>
<td>7.14 (1.5)</td>
<td>7.13 (1.7)</td>
<td>7.14 (1.6)</td>
</tr>
<tr>
<td>Baseline NRS pain score, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain location</td>
<td>15 (71)</td>
<td>15 (65)</td>
<td>30 (68)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>4 (19)</td>
<td>8 (35)</td>
<td>12 (27)</td>
</tr>
<tr>
<td>Extremity</td>
<td>2 (10)</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

All results reported as no. (%) unless otherwise indicated. BPM, beats per minutes; RPM, respirations per minutes.

### Table 2

<table>
<thead>
<tr>
<th>Time</th>
<th>Morphine (95% CI)</th>
<th>Low-dose ketamine (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T5</td>
<td>−3 (−3.9, −2.1)</td>
<td>−4.9 (−5.8, −4)</td>
</tr>
<tr>
<td>T10</td>
<td>−3.4 (−4.4, −2.5)</td>
<td>−4.3 (−5.5, −3.1)</td>
</tr>
<tr>
<td>T20</td>
<td>−3.3 (−4.4, −2.2)</td>
<td>−3.2 (−4.4, −2.1)</td>
</tr>
<tr>
<td>T40</td>
<td>−4.5 (−5.6, −3.5)</td>
<td>−3.7 (−5.2, −2.3)</td>
</tr>
<tr>
<td>T60</td>
<td>−4.8 (−5.6, −3.8)</td>
<td>−3.5 (−5.4, −1.6)</td>
</tr>
<tr>
<td>T80</td>
<td>−4.4 (−5.9, −2.9)</td>
<td>−3.9 (−6.1, −1.6)</td>
</tr>
<tr>
<td>T100</td>
<td>−5 (−6.6, −3.5)</td>
<td>−4.1 (−6.8, −1.5)</td>
</tr>
<tr>
<td>T120</td>
<td>−5 (−7.1, −2.9)</td>
<td>−3.6 (−6.1, −1)</td>
</tr>
</tbody>
</table>

T5 was 5 minutes after drug administration. T120 was 120 minutes after drug administration and end of our observation period. Bolded texts emphasize time of maximum change in NRS pain score from baseline for each group: morphine (T100) and low-dose ketamine (T5).

**Fig. 2.** Numeric rating scale pain score (mean, SD) as percent change from baseline over time by treatment group. There were no significant differences at any time point.
vomited. One patient in the morphine arm was treated for pruritus. Three patients in the ketamine group experienced hallucinations. No dissociation or emergency reactions were detected. Neither midazolam nor naloxone was given during the study.

The median provider satisfaction score was 4 (interquartile range \([IQR]\), 3-5) for the low-dose ketamine group and 4 (IQR, 4-5) for the morphine group (Table 5). The average nursing score was 4 (IQR, 3-5) for the low-dose ketamine group and 5 (IQR, 4-5) for the morphine group (Table 6).

4. Discussion

Low-dose ketamine was not superior to morphine in the maximum change of NRS pain scores from baseline. However, if alternatives to opioids are going to be prescribed for acute pain in the ED, the analgesic potential of the alternatives must be comparable to opioids. Our study demonstrates that ketamine may have comparable analgesic effects; however, more studies are needed.

The maximum reduction in pain scores for low-dose ketamine was seen immediately after the infusion was complete and was sustained for only 5 to 10 minutes. In the morphine group, a similar maximum reduction in pain scores was reached 100 minutes after the infusion was complete. The rapid decrease in pain provided by low-dose ketamine is an advantage compared with morphine for the treatment of acute pain in the ED. However, the inability to sustain this degree of pain relief over the normal course of an ED stay may require higher doses of low-dose ketamine infused over a longer duration or the use of adjunctive medications.

The short duration of maximum analgesia likely contributed to the increased rate of repeat dosing in the ketamine arm (54%) vs the morphine arm (38%), although the difference was not statistically significant.

In the ketamine group, 25% of the patients did not complete the entire 120 minutes of data collection (assessments were stopped for inadequate pain control if the patients requested a third dose of the study drug). These 2 outcomes highlight the poor sustained maximum analgesia of low-dose ketamine. However, as mentioned above, the safest and most effective dose for low-dose ketamine has yet to be established. In addition, because most patients in the ketamine arm received a total of 0.6 mg/kg (0.3 mg/kg × 2 separated by at least 20 minutes), a higher initial dose infused over a longer period of time could lengthen the duration of maximum analgesia. Additional prospective studies to evaluate this approach are needed.

Despite the inability of low-dose ketamine to sustain its maximum analgesic effect, there was greater than 50% reduction in pain scores for 2 hours at all intervals, after T20. As stated above, 25% of the patients did not complete the entire 120-minute observation period, and the majority needed a repeat dose of ketamine. However, an alternate medication to opioids that can provide a greater than a 50% decrease in acute pain for 2 hours is valuable for clinical use.

We also collected provider and nurse satisfaction scores after completion of the patient’s observation period. Both drugs scored similarly with both the providers and the nurses. The nursing group was slightly more satisfied with morphine; however, this trend was not clinically significant. Future studies should further evaluate this trend.

In addition to the similarities in pain control between low-dose ketamine and morphine, low-dose ketamine was comparable to

### Table 3
Repeat dosing of analgesia reported by treatment group

<table>
<thead>
<tr>
<th></th>
<th>Morphine</th>
<th>Low-dose ketamine</th>
<th>(P)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second dose, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (38)</td>
<td>13 (54)</td>
<td>.37(^a)</td>
<td>21 (47)</td>
</tr>
<tr>
<td>No</td>
<td>13 (62)</td>
<td>11 (46)</td>
<td></td>
<td>24 (53)</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>24</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Third dose, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (14)</td>
<td>6 (25)</td>
<td>.47(^b)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>No</td>
<td>18 (86)</td>
<td>18 (75)</td>
<td></td>
<td>36 (80)</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>24</td>
<td></td>
<td>45</td>
</tr>
</tbody>
</table>

\(^a\) \chi^2 Test.

\(^b\) Fisher exact test.
morphine regarding adverse effects as well. We detected a similar adverse effect rate (57% vs 58%) and RASS scores in both arms. Vital signs were similar as well, although there were statistically significant differences in systolic and diastolic blood pressure between the groups. These differences were secondary to both decreases in blood pressure in the morphine group and increases in blood pressure in the low-dose ketamine group. These findings are established effects of these medications and should be anticipated, but are of minimal clinical significance. We did observe dysphoria (4) and hallucinations (3) only in the ketamine arm. These effects should be anticipated with low-dose ketamine. However, no episodes of dissociation or emergence reactions were detected. We specifically did not detect more hypoxia, bradycardia, or sedation in the morphine group.

Our results are similar to prior studies that evaluated low-dose ketamine alone for the treatment of pain. Hirlinger and Pfenninger [27] demonstrated a decrease in pain scores with 5 minutes of infusion in ED patients receiving IV low-dose ketamine (0.25 or 0.5 mg/kg) for acute musculoskeletal injuries. However, this study lacked a control arm. The 0.3-mg/kg dose in the study by Persson et al [28] decreased pain scores immediately, with the effect starting to decrease at 20 minutes after infusion, which was similar to our results. In addition, the patients in this study, although they had chronic and not acute pain, experienced a greater than 50% decrease in pain scores for 1 hour after infusion, just as in our study. Persson et al also compared low-dose ketamine to morphine and showed a similar delayed but prolonged analgesic effect.

Fig. 6. Mean pulse rate over time with SD. There were no significant differences at any time point.

Fig. 7. Mean respiratory rate over time with SD. There were no significant differences at any time point.

Fig. 8. Mean oxygen saturation over time with SD. There were no significant differences at any time point.

Table 4
Adverse effects reported by total events

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Morphine (n = 8)</th>
<th>Low-dose ketamine (n = 12)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Lightheaded</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Decreased oxygen saturation</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Numbness</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>14</td>
<td>26</td>
</tr>
</tbody>
</table>

n = number of patients experiencing an adverse effect. Some patients reported multiple adverse effects.

Our study was not the first to evaluate low-dose ketamine in the ED, but it is unique [8,27,29,30]. Although other ED studies have evaluated low-dose ketamine as an adjunct to opioid therapy [29,30], as the sole agent without comparison [27], and in a retrospective case series [8], to our knowledge, this is the first randomized, double-blinded study to compare low-dose ketamine to morphine for acute pain in the ED. In addition, we evaluated low-dose ketamine for the treatment of multiple types of pain (trauma, medical) and at multiple anatomical sites (abdomen, back, extremity). Most studies with low-dose ketamine in the ED and prehospital setting have evaluated its use in acute traumatic or musculoskeletal pain [18,27,30,31]. Another unique aspect of this study was the use of the RASS score to capture the cognitive and behavioral effects of the study drugs, although we saw no difference between groups.

4.1. Limitations

There were several limitations to our study. Our study was conducted at a military medical center, which has the potential to limit the generalizability of its results. However, only ≈20% of the ED patients are uniformed active military service members. Most of the patients are civilians who have similar demographic characteristics compared with other civilian EDs at a level 1 trauma and tertiary care centers. In addition, the generalizability of our results may be limited, as our data were collected from a single medical center.
Our study has a small sample size. Our study required a number of very specific inclusion and exclusion criteria as it was a prospective pain study and one of the study drugs (ketamine) was otherwise used almost exclusively for procedural sedation. In addition, the number of patients who were able to complete an adequate screening and enrollment process while experiencing moderate to severe acute pain further limited our study population.

We calculated our sample size to detect a 2-point difference in the maximum change from baseline between the 2 groups. Detecting a 2-point difference in NRS pain scores is greater than what some authors have reported as clinically significant (eg, an NRS difference of 1.3) [32]. We reported a 0.1 difference in the maximum change in NRS pain scores between the 2 groups. A larger number of patients would have provided more precise data to allow us to determine if a larger difference between NRS pain scores was detectable. However, given the small difference between the 2 groups in our study, an argument for a similar clinical effect can be made, although our study was not powered to demonstrate this.

The analgesic dose of ketamine is not standardized. We administered ketamine at a dose of 0.3 mg/kg. Several studies have reported the use of “low-dose ketamine,” but there are many differences in the dose and the mode of delivery (IM vs IV) between the studies [15–18,27,28,31,33]. The studies by Hirlinger and Pfenninger [27] and Persson et al [28] provided the best data to guide our dosing. Both studies correlated IV ketamine dose with plasma levels of ketamine. Hirlinger and Pfenninger compared 0.25 and 0.5 mg/kg of ketamine in trauma patients in the ED. Persson et al compared 0.15, 0.3, and 0.45 mg/kg in patients with chronic ischemic pain due to lower extremity arteriosclerosis obliterans. Both studies cited impairment or adverse neurologic effects with the highest dose. Pain control was adequate, and these neurologic effects were not seen at the 0.25- and 0.3-mg/kg dosage. However, there are no large trials with data to support a specific dose that maximizes analgesia and avoids neurologic adverse effects.

Our measure of sedation and agitation has not been validated in the ED. The RASS is a validated tool used in the intensive care unit setting to evaluate sedation, etc. The RASS score was the best tool that we found for objective scoring system that could be used to evaluate all patients, regardless of the study drug they received. In addition, this tool allowed us to quantify and provide a time course for some of the more clinically significant adverse reactions associated with these medications (hallucinations, altered sensorium, agitation, emergence, sedation, etc). The RASS score was the best tool that we found for capturing the adverse effects of both drugs; however, its reliability and validity have not been established in the population of patients enrolled in this study.

We did not obtain serum levels for the drug administered during our study. As mentioned above, prior studies have done this [27,28]. These data would have been helpful to make more specific correlations with the study drugs and their effects on pain scores and adverse reactions.

We did not obtain long-term follow up. We do not know if there was a difference in the number of patients who returned to the ED for treatment of the same pain after their initial encounter. These outcomes should be evaluated in future ED studies involving low-dose ketamine and morphine for acute pain.

Finally, we did not include patients with chronic pain. This is a patient population that frequents the ED. However, the analgesic effects as well as adverse effects of ketamine or morphine in this population may be different.

5. Conclusions

In ED patients with acute, moderate-severe pain, low-dose ketamine did not provide a superior maximum reduction in NRS pain scores compared with morphine. However, these 2 medications produced similar adverse effects, as well as provider and nurse satisfaction scores. In addition, low-dose ketamine induced analgesic effects within 5 minutes of infusion and provided a moderate reduction in pain for 2 hours.

Acknowledgments

We would have been unable to complete this study without the contributions of Steve Ray, RN, CNS; Sarah Abel, RN, CNS; and Leean Zarzabal. We thank Steve Ray, RN, CNS, and Sarah Abel, RN, CNS, for their support of the trial and Leean Zarzabal for statistical support.

References


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Intravenous Subdissociative-Dose Ketamine Versus Morphine for Analgesia in the Emergency Department: A Randomized Controlled Trial

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Study objective: We assess and compare the analgesic efficacy and safety of subdissociative intravenous-dose ketamine with morphine in emergency department (ED) patients.

Methods: This was a prospective, randomized, double-blind trial evaluating ED patients aged 18 to 55 years and experiencing moderate to severe acute abdominal, flank, or musculoskeletal pain, defined as a numeric rating scale score greater than or equal to 5. Patients were randomized to receive ketamine at 0.3 mg/kg or morphine at 0.1 mg/kg by intravenous push during 3 to 5 minutes. Evaluations occurred at 15, 30, 60, 90, and 120 minutes. Primary outcome was reduction in pain at 30 minutes. Secondary outcome was the incidence of rescue analgesia at 30 and 60 minutes.

Results: Forty-five patients per group were enrolled in the study. The primary change in mean pain scores was not significantly different in the ketamine and morphine groups: 8.6 versus 8.5 at baseline (mean difference 0.1; 95% confidence interval −0.46 to 0.77) and 4.1 versus 3.9 at 30 minutes (mean difference 0.2; 95% confidence interval −1.19 to 1.46; P=0.97). There was no difference in the incidence of rescue fentanyl analgesia at 30 or 60 minutes. No statistically significant or clinically concerning changes in vital signs were observed. No serious adverse events occurred in either group.

Patients in the ketamine group reported increased minor adverse effects at 15 minutes post-drug administration.

Conclusion: Subdissociative intravenous ketamine administered at 0.3 mg/kg provides analgesic effectiveness and apparent safety comparable to that of intravenous morphine for short-term treatment of acute pain in the ED. [Ann Emerg Med. 2015;66:222–229.]

Please see page 223 for the Editor’s Capsule Summary of this article.

INTRODUCTION

Background

The provision of adequate, safe, and timely analgesia is a core component of patient care in the emergency department (ED). Ketamine is a noncompetitive N-methyl-D-aspartate and glutamate receptor antagonist that decreases central sensitization, “wind-up” phenomena, and pain memory.1,2 As a phencyclidine-like dissociative agent, ketamine possesses a number of pharmacologic characteristics useful to the emergency physician. At doses commonly used for procedural sedation (1 to 1.5 mg/kg), ketamine produces a trancelike cataleptic state, whereas at subdissociative doses (0.1 to 0.6 mg/kg; most commonly 0.3 mg/kg) it maintains potent analgesic and amnestic effects that are accompanied by preservation of protective airway reflexes, spontaneous respiration, and cardiopulmonary stability.3,5

Importance

In subdissociative doses, ketamine has been shown to confer potent, opioid-sparing effects and to be effective in providing analgesia for pain that is poorly controlled by opioids in a variety of settings outside of the ED.6–9 Emerging data on the use of subdissociative-dose ketamine as a single agent in out-of-hospital and austere settings, where it has compared favorably to morphine, support a role for ketamine in the analgesic armamentarium of emergency physicians. Two retrospective studies demonstrated that subdissociative-dose ketamine in the dosing range of 0.1 to 0.6 mg/kg, when administered as an
adjunct to opioid analgesics, significantly reduced pain reported by patients in the ED.10,11

Goals of This Investigation
In our study, we hypothesize that a subdissociative dose of ketamine administered as a single agent at 0.3 mg/kg will provide relief similar to that of a standard dose of morphine at 0.1 mg/kg for acute moderate to severe pain in the ED setting. The primary outcome used to test our hypothesis is the comparative reduction in participants’ pain scores at 30 minutes from medication administration.

MATERIALS AND METHODS
Study Design
This was a prospective, randomized, double-blind trial comparing the safety and efficacy of subdissociative intravenous-dose ketamine with intravenous morphine for acute pain in the ED. This study was approved by the Maimonides Medical Center institutional review board and registered with clinicaltrials.gov (NCT01835262). The study was conducted and is reported according to the Consolidated Standards of Reporting Trials Group.12

Study Setting and Selection of Participants
The study facility is a 711-bed community teaching hospital with an annual ED census of more than 120,000 visits. Patient screening, enrollment, and data collection were performed by a study investigator (B.R., I.P., and V.T.). ED pharmacy investigators maintained the randomization list, which was generated before commencement of the study, prepared the medication, and delivered it to the nurse caring for the study participant in a blinded manner.

A convenience sample of patients was enrolled between June 2013 and May 2014. Enrollment occurred at various times of the day when both a study investigator was available for patient enrollment and an ED pharmacist was available for medication preparation.

The study included patients aged 18 to 55 years who presented to the ED with acute abdominal, flank, back, or musculoskeletal pain score of 5 or more on a standard 11-point (0 to 10) numeric rating scale and required opioid analgesia, as determined by the treating attending physician.13,14 Acute pain was defined as having an onset within 7 days. Exclusion criteria included pregnancy, breast-feeding, altered mental status, allergy to morphine or ketamine, weight less than 46 kg or greater than 115 kg, unstable vital signs (systolic blood pressure <90 or >180 mm Hg, pulse rate <50 or >150 beats/min, and respiration rate <10 or >30 breaths/min), and medical history of acute head or eye injury, seizure, intracranial hypertension, chronic pain, renal or hepatic insufficiency, alcohol or drug abuse, psychiatric illness, or recent (4 hours before) opioid use.

Each patient was approached by a study investigator for acquisition of written informed consent and Health Insurance Portability and Accountability Act authorization after being evaluated by the treating emergency physician and determined to meet study eligibility criteria.

In situations in which English was not the participant’s primary language, a staff interpreter or licensed telephone interpreter was used. Baseline pain score was determined with an 11-point numeric rating scale (0 to 10), described to the patient as “no pain” being 0 and “the worst pain imaginable” being 10. A patient was eligible for enrollment if a baseline numeric rating scale score of 5 or greater was reported. A study investigator then recorded the patient’s body weight and baseline vital signs.

The on-duty ED pharmacist prepared 0.3 mg/kg of ketamine or 0.1 mg/kg of morphine in 10 mL of normal saline solution according to the predetermined randomization list, which was created in SPSS (version 19.0; IBM Corp, Armonk, NY) with block randomization every 10 participants, up to 90. The medication was delivered to the treating nurse in a blinded fashion and was
administered by intravenous push during 3 to 5 minutes. The preparing pharmacist, research manager, and statistician were the only members of the team with knowledge of the study arm to which the participant was randomized, leaving the providers, participants, and data-collecting research team blinded to the medication received. Study investigators recorded pain scores, vital signs, and adverse effects at 15, 30, 60, 90, and 120 minutes. If patients reported a pain numeric rating scale score of 5 or greater and requested additional pain relief, fentanyl 1 μg/kg was administered as a rescue analgesic. Blinding of the patient, research team, and clinical staff was strictly maintained by the on-duty ED pharmacist.

All data recorded on data collection sheets, including sex, demographics, medical history, and vital signs, were entered into SPSS (version 19.0; IBM Corp) by the research manager. Development of the randomization list, confirmation of written consent acquisition for all participants, and statistical analyses were conducted by the research manager and statistician, who were independent of any data collection.

**Outcome Measures**

The primary outcome was comparative reduction of numeric rating scale pain scores between recipients of ketamine and morphine at 30 minutes. The secondary outcome was need for rescue analgesia at either 30 or 60 minutes. Vital sign changes and adverse events were also analyzed.

**Primary Data Analysis**

Data analyses included frequency distributions, paired t test to assess a difference in pain scores within each group, and independent-sample t test to assess differences in pain scores between the 2 groups at the various intervals (SPSS, version 19.0; IBM Corp). Mixed-model linear regression (SAS, version 9.1; SAS Institute, Inc., Cary, NC) was used to compare changes in pain numeric rating scale across time points. This compensated for participants lost to follow-up and allowed all patients’ data to be analyzed on an intention-to-treat principle. A mean contrast test based on the mixed-model linear regression results compared the primary outcome difference at 30 minutes relative to time 0. The 95% confidence limits for the mean difference in numeric rating scale pain score for the ketamine versus morphine groups at each time point were calculated with 2 estimate methods for the pooled SD. One method was based on the pooled SD from the bivariate t test comparison at each specific time point, whereas the other method was based on the pooled SD from the repeated-measures ANOVA. The latter method uses data at all time points and provides a more reliable estimate of the SD. For categorical outcomes (eg, complete resolution of pain), a \( \chi^2 \) or Fisher’s exact test was used to compare rates for categorical outcomes at 30 minutes. Percentage differences and 95% confidence limits between the treatment groups were calculated for all time points. \( P<.05 \) was used to denote statistical significance.

In accordance with the validation by Bijur et al \(^1\) of a verbally administered rating scale of acute pain in the ED and the comparison by Holdgate et al \(^2\) of verbal and visual pain scales, we assumed a primary outcome consisting of a minimal clinically meaningful difference of 1.3 between the ketamine and morphine groups at the 30-minute pain assessment. Assuming an SD of 3.0, a power analysis determined that a repeated-measures ANOVA with a sample size of 90 (45 in each group) provided at least 83% power to detect a difference of at least 1.3 at 30 minutes (as well as at any other interval postbaseline), with an \( \alpha = .05 \).

**RESULTS**

Ninety patients (45 ketamine and 45 morphine) were enrolled in the study. The patients’ mean age was 35 and 36 years, respectively (SD=10 for both groups); 67% and 62% were women, respectively. There were no differences between the groups in terms of demographic characteristics or baseline vital signs, pain scores, or chief complaint (Table 1). The patient flow diagram is illustrated in Figure 1.

As shown in Table 2, patients’ reported pain scores at time 0 were similar in the 2 groups: the mean difference in pain numeric rating scale score for ketamine versus morphine was 0.1 (95% confidence interval [CI] –0.46 to 0.77). Participants received an average dose of either

<table>
<thead>
<tr>
<th>Table 1. Demographics and clinical characteristics of patients at enrollment.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
</tr>
<tr>
<td>Female, No. (%)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
</tr>
<tr>
<td><strong>Blood pressure, mean (SD), mm Hg</strong></td>
</tr>
<tr>
<td>Systolic</td>
</tr>
<tr>
<td>Diastolic</td>
</tr>
<tr>
<td>Pulse rate, beats/min</td>
</tr>
<tr>
<td><strong>Source of pain, No. (%)</strong></td>
</tr>
<tr>
<td>Abdominal</td>
</tr>
<tr>
<td>Flank</td>
</tr>
<tr>
<td>Other*</td>
</tr>
</tbody>
</table>

*Other pain sources include back and musculoskeletal pain.
21.8 mg (SD=4.9) of ketamine or 7.7 mg (SD=1.6) of morphine. All patients showed significant reductions in mean pain numeric rating scale score at 15 and 30 minutes compared with baseline. However, there were no statistically significant differences between the 2 groups at either point. At 15 minutes, the mean difference in pain numeric rating scale score was –1.0 (95% CI –2.40 to 0.31). At 30 minutes, the primary outcome comparison, the mean difference, was 0.2 (95% CI –1.19 to 1.46; P=.97). The 95% CI for the mean difference at 30 minutes according to the mixed-model regression SD was –0.77 to 1.05. The parallel line plots (Figure 2) presenting the changes in pain numeric rating scale score for each group from baseline to 30 minutes show almost the same pattern of decrease, with the exception of 1 patient in the ketamine group who showed an increase from 9 to 10. The box plots of the difference likewise show a similar pattern of central tendency and dispersion. As shown in Figure 3, comparison of the pain scores over all time points demonstrates similar mean pain numeric rating scale scores in the 2 study groups.

At 15 minutes, more patients reported complete resolution of pain (numeric rating scale=0) in the ketamine group (percentage difference=31%; 95% CI 13% to 49%). However, this difference was no longer present at 30 minutes (percentage difference=3%; 95% CI –16% to 21%). All of the patients who reported complete resolution of pain did so with the analgesic benefit of the study medication and without the use of a rescue analgesic dose of fentanyl during these measurement intervals. There were no statistically significant differences between the groups in the proportion of patients reporting a 3-point or more reduction in pain numeric rating scale score. There was also no significant difference between the 2 groups with respect to use of rescue fentanyl analgesia at 30 minutes (percentage difference=7%; 95% CI –3% to 16%) or at 60 minutes (percentage difference=5%; 95% CI –18% to 9%). At 120 minutes, the ketamine group required significantly more rescue fentanyl (percentage difference=17%; 95% CI 1% to 34%) (Table 2).

No serious or life-threatening adverse events occurred in either medication group; these included, but were not limited to, respiratory distress, seizures, and cardiac arrest. There were no changes in vital signs that were clinically concerning or required intervention (Table E1, available online at http://www.annemergmed.com). All adverse effects were transient and did not require treatment.

A statistically significant difference was observed in the number of ketamine patients who reported any adverse effects immediately after the medication injection and at 15 minutes (percentage difference=38%; 95% CI 18% to 57%). This difference in adverse effects diminished to
Table 2. Pain trends.

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Group</th>
<th>Pain NRS, mean (SD)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ketamine</td>
<td>Morphine</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.6 (1.5)</td>
<td>8.5 (1.5)</td>
<td>0.1 (−0.46 to 0.77)</td>
</tr>
<tr>
<td>15</td>
<td>3.2 (3.5)</td>
<td>4.2 (2.9)</td>
<td>−1.0 (−2.40 to 0.31)</td>
</tr>
<tr>
<td>30</td>
<td>4.1 (3.2)</td>
<td>3.9 (3.1)</td>
<td>0.2 (−1.19 to 1.46)</td>
</tr>
<tr>
<td>60</td>
<td>4.8 (3.2)</td>
<td>3.4 (3.0)</td>
<td>1.4 (0.13 to 2.75)</td>
</tr>
<tr>
<td>90</td>
<td>4.8 (3.1)</td>
<td>3.9 (3.1)</td>
<td>0.9 (−0.37 to 2.28)</td>
</tr>
<tr>
<td>120</td>
<td>3.9 (2.9)</td>
<td>3.7 (2.9)</td>
<td>0.2 (−1.09 to 1.46)</td>
</tr>
<tr>
<td>Complete resolution of pain, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>20 (44)</td>
<td>6 (13)</td>
<td>31 (13.1 to 49.2)</td>
</tr>
<tr>
<td>30</td>
<td>12 (27)</td>
<td>11 (24)</td>
<td>3 (−16.3 to 20.7)</td>
</tr>
<tr>
<td>60</td>
<td>9 (21)</td>
<td>12 (27)</td>
<td>−6 (−25.6 to 11.6)</td>
</tr>
<tr>
<td>90</td>
<td>7 (16)</td>
<td>9 (21)</td>
<td>−5 (−21.5 to 12.2)</td>
</tr>
<tr>
<td>120</td>
<td>9 (22)</td>
<td>9 (21)</td>
<td>1 (−17.7 to 18.8)</td>
</tr>
<tr>
<td>Reduction of 3+ NRS, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>34 (75)</td>
<td>31 (69)</td>
<td>6 (−12.3 to 25.6)</td>
</tr>
<tr>
<td>30</td>
<td>33 (73)</td>
<td>31 (69)</td>
<td>4 (−14.7 to 23.6)</td>
</tr>
<tr>
<td>60</td>
<td>25 (58)</td>
<td>33 (77)</td>
<td>−19 (−38.5 to 1.3)</td>
</tr>
<tr>
<td>90</td>
<td>23 (54)</td>
<td>33 (77)</td>
<td>−23 (−43.3 to −3.2)</td>
</tr>
<tr>
<td>120</td>
<td>29 (71)</td>
<td>33 (79)</td>
<td>−8 (−27.0 to 11.3)</td>
</tr>
<tr>
<td>Fentanyl rescue incidence, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>4 (9)</td>
<td>1 (2)</td>
<td>7 (−2.9 to 16.3)</td>
</tr>
<tr>
<td>60</td>
<td>4 (9)</td>
<td>6 (14)</td>
<td>−5 (−18.1 to 9.0)</td>
</tr>
<tr>
<td>90</td>
<td>5 (11)</td>
<td>5 (12)</td>
<td>−1 (−13.1 to 14.1)</td>
</tr>
<tr>
<td>120</td>
<td>12 (29)</td>
<td>5 (12)</td>
<td>17 (0.8 to 34.2)</td>
</tr>
</tbody>
</table>

NRS, Numeric rating scale.

*Minutes from time of medication injection.

**95% CI −0.77 to 1.05 is based on the SD from the mixed-model regression.

 equivalence with morphine at the 30-minute interval (Table 3). The most common adverse effects reported by ketamine patients were dizziness, disorientation, mood changes, and nausea. Dizziness and nausea were also reported by morphine patients.

LIMITATIONS

This was a single-center study in which patients were enrolled as a convenience sample according to predetermined inclusion and exclusion criteria. Sample size was near minimum for adequate power (80%). There was a potential for unblinding because some participants exhibited ketamine-specific reactions such as nystagmus. Patient enrollment was restricted to time frames in which both a member of the research team and pharmacy team were available.

DISCUSSION

Subdissociative ketamine has been shown to mitigate pain and reduce opioid consumption in patients with chronic pain (neuropathic pain), cancer pain, and acute postoperative pain, as demonstrated in the anesthesia and surgical literature. There have been several published retrospective studies and prospective trials examining ketamine used for analgesia in ED patients. Lester et al evaluated 35 patients who received subdissociative ketamine for analgesia and reported that 19 patients (54%) experienced pain relief after opioid analgesics had failed. Richards and Rockford evaluated 24 patients who received subdissociative ketamine and reported an overall reduction in pain score of 5 points (8.9 [SD=2.1] to 3.9 [SD=3.4]); however, 18 patients (75%) had received opioid analgesics before ketamine. In addition, 55% of patients reported satisfaction with subdissociative ketamine analgesia and 67% stated that they would choose ketamine analgesia again. Neither study reported significant adverse effects in the ketamine recipients. Several prospective randomized trials examined the analgesic effect of subdissociative ketamine and morphine combination on patients with traumatic and nontraumatic pain. An out-of-hospital study by Johansson et al demonstrated statistical improvement in pain reduction by 4.4 points with the use of morphine-ketamine combination in comparison to 3.1 points with morphine alone. The 3-arm trial by Beaudoin et al that evaluated 2 different doses of subdissociative ketamine-morphine combinations compared with morphine alone for ED analgesia showed a clinically significant decrease in pain intensity for more than 50% of patients who received morphine (0.1 mg/kg) and ketamine (0.15 or 0.3 mg/kg) combination compared with the morphine-only group. In addition, the authors concluded that morphine combined with ketamine at a dose of 0.3 mg/kg had more efficacious analgesic effect than a combination using a ketamine dose of 0.15 mg/kg. Last, Miller et al conducted the first randomized controlled superiority trial directly comparing subdissociative ketamine to morphine for acute pain in the ED. The results showed that ketamine administered at a dose of 0.3 mg/kg ketamine did not provide a superior maximum reduction in numeric rating scale pain scores compared with morphine at 0.1 mg/kg.

In our prospective, randomized, double-blind trial, we compared single subdissociative-dose ketamine with single-dose morphine for ED patients experiencing acute severe pain. Our study suggests that subdissociative ketamine is as effective as morphine in relieving pain at 15 and 30 minutes. The subdissociative ketamine group had a larger proportion of patients who reported complete resolution of pain (numeric rating scale score=0), without the use of analgesic fentanyl rescue, at 15 minutes (44% versus 13%); however, there was no difference between the groups in pain resolution or change in pain scores at 30 minutes. There was...
also no difference in the proportion of patients who reported a 3-point or more reduction in pain numeric rating scale score at either interval. These findings suggest that subdissociative ketamine is as effective as morphine in the reduction of acute pain within 15 minutes of administration.

No participants in either group experienced clinically concerning adverse events or changes in vital signs. However, the subdissociative ketamine recipients did experience a statistically significant increase in adverse effects immediately postinjection and at the 15-minute interval, with high percentages of participants experiencing dizziness and disorientation compared with the morphine recipients.

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Group</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report of any adverse effect</td>
<td>Ketamine</td>
<td>Morphine</td>
</tr>
<tr>
<td>Postinjection</td>
<td>33 (73)</td>
<td>23 (51)</td>
</tr>
<tr>
<td>15 min</td>
<td>31 (69)</td>
<td>14 (31)</td>
</tr>
<tr>
<td>30 min</td>
<td>16 (36)</td>
<td>15 (33)</td>
</tr>
<tr>
<td>Most common adverse effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postinjection</td>
<td>24 (53)</td>
<td>14 (31)</td>
</tr>
<tr>
<td>15 min</td>
<td>19 (42)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>30 min</td>
<td>8 (18)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Disorientation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postinjection</td>
<td>13 (29)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>15 min</td>
<td>5 (11)</td>
<td>0</td>
</tr>
<tr>
<td>30 min</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Mood changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postinjection</td>
<td>6 (13)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>15 min</td>
<td>5 (11)</td>
<td>0</td>
</tr>
<tr>
<td>30 min</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postinjection</td>
<td>4 (9)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>15 min</td>
<td>8 (18)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>30 min</td>
<td>6 (13)</td>
<td>9 (20)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%)
These findings are consistent with those of previous trials of ketamine and opioid combination regimens. Ahern et al.24 found that 24 of 30 out-of-hospital patients (80%) receiving an intravenous combination of hydromorphone (0.5 mg) and ketamine (15 mg) experienced an adverse effect, with dizziness being the most common. These results were observed again in the study by Beaudoin et al.,22 in which 9 of 20 (45%) of the morphine (0.1 mg/kg) and ketamine (0.3 mg/kg) group reported lightheadedness or dizziness. We believe further investigation of ketamine dose ranges and duration of infusion will help to diminish the adverse effects experienced by patients while maintaining analgesic efficacy similar to that of morphine.

Subdissociative-dose intravenous ketamine administered at 0.3 mg/kg provides analgesic effectiveness and apparent safety comparable to that of intravenous morphine for short-term treatment of acute moderate to severe pain in the ED.

The authors acknowledge John Marshall, MD, for his support and guidance; Cierra Treu, PharmD, Anil Jacob, PharmD, and Erica Colgan, PharmD, for medication administration to study patients; and Tamar Motov, RN, and Nicolette Tedeschi, RN, for assistance with patient screening and enrollment.

Supervising editor: Steven M. Green, MD

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Author contributions: SM, VT, IP, AL, ES-Z, and CF conceived the study, designed the trial, and obtained research funding. SM, BR, AL, and CF supervised the conduct of the trial and data collection. BR, IP, CM, and VT undertook recruitment of patients and managed the data, including quality control. AL and PH provided statistical advice on study design and data analysis. BR drafted the article, and all authors contributed substantially to its revision. SM takes responsibility for the paper as a whole.

Funding and support: By Annals policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist and provided the following details: This research was funded, in part, by an unrestricted grant from the New York Department of Health’s Empire Clinical Research Investigator Program.


REFERENCES


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**Images in Emergency Medicine**

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

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

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.]

0196-0644/$-see front matter
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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.

of circulating catecholamines to increase bronchodilation, blocking calcium influx, and directly relaxing smooth muscle by reducing vagally mediated bronchoconstriction.

Importance
The reported efficacy of a ketamine infusion in children has been previously limited to case reports. In 1971, Betts and Parkin 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. Sarma later reported avoiding intubation in 2 adults using a ketamine infusion of 0.15 mg/kg per hour, whereas Nehama et al 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.

One randomized trial by Howton et al 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 nonsedation 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 Index 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. 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 ensure 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. χ² Analysis was performed on categoric variables between groups. At the completion of enrollment, an analysis of covariance was performed to examine the interaction of

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**Table 1.** Pulmonary Index.

<table>
<thead>
<tr>
<th>Score</th>
<th>&lt;6 y</th>
<th>&gt;6 y</th>
<th>Wheezing</th>
<th>Inspiratory/Expiratory Ratio</th>
<th>Accessory Muscle Use</th>
<th>Oxygen Saturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;30</td>
<td>&lt;20</td>
<td>None</td>
<td>2:1</td>
<td>None</td>
<td>99%–100%</td>
</tr>
<tr>
<td>1</td>
<td>31-45</td>
<td>21-35</td>
<td>End expiration</td>
<td>1:1</td>
<td>+</td>
<td>96%–98%</td>
</tr>
<tr>
<td>2</td>
<td>46-60</td>
<td>36-50</td>
<td>Entire expiration</td>
<td>1:2</td>
<td>++</td>
<td>93%–95%</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>
<td>&lt;93%</td>
</tr>
</tbody>
</table>
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 guidelines 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 0.4; 95% CI −0.4 to 1.3). 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. 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 guidelines 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.

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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>Asian</td>
<td>3 (8.6%)</td>
<td>3 (9.1%)</td>
<td>0.5%</td>
<td>−13% to 14%</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 (85.7%)</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

![Figure 1. Patient flow algorithm.](image)

![Figure 2. Mean improvement in Pulmonary Index score, with SD shown at each point during infusion. PI, Pulmonary Index.](image)
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.

Figure 3. This is a parallel line plot showing the change in Pulmonary Index score by subject. There are 33 patients on the left of the dividing line who received ketamine and 35 patients on the right who received the placebo infusion. The marker ■ signifies the Pulmonary Index score at time 0 for each patient. The vertical line emanating from each marker displays its change over the time during which the patients received the infusion.

Figure 4. This is a parallel line plot showing the change in Pulmonary Index score by subject. There are 33 patients on the left of the dividing line who received ketamine and 35 patients on the right who received the placebo infusion. The marker ■ signifies the Pulmonary Index score at time 0 for each patient. The vertical line emanating from each marker displays its change over the time during which the patients received the infusion.

Table 4. Disposition of enrolled patients.

<table>
<thead>
<tr>
<th>Disposition, No. (%)</th>
<th>Placebo (N=35)</th>
<th>Ketamine (N=33)</th>
<th>Difference in Proportions</th>
<th>95% CI for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home</td>
<td>6 (17%)</td>
<td>7 (21%)</td>
<td>4%</td>
<td>−14% to 22%</td>
</tr>
<tr>
<td>General ward</td>
<td>18 (51%)</td>
<td>13 (39%)</td>
<td>12%</td>
<td>−10% to 35%</td>
</tr>
<tr>
<td>Intermediate care unit</td>
<td>10 (29%)</td>
<td>10 (30%)</td>
<td>1%</td>
<td>−18% to 20%</td>
</tr>
<tr>
<td>ICU</td>
<td>1 (3%)</td>
<td>3 (9%)</td>
<td>6%</td>
<td>−9% to 21%</td>
</tr>
</tbody>
</table>
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 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 that the dosing regimens (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.

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REFERENCES

Intravenous ketamine to facilitate noninvasive ventilation in a patient with a severe asthma exacerbation

Abstract

Despite advances in outpatient treatment and an improved understanding of the pathophysiology, asthma continues to be a significant source of morbidity and mortality in the United States. Although there is certainly a component of chronic inflammation, the majority of the symptoms in acute asthma exacerbations can be reversed with proper medications and management. Reversing bronchoconstriction and avoiding mechanical ventilation should be the goals of the emergency physician and the intensivist to avoid intubation and to view this intervention as a last resort.

We describe a case of ketamine administration and utilization of noninvasive positive pressure ventilation (NIPPV) to avoid mechanical ventilation in a patient with a severe asthma exacerbation.

A 36-year-old man in extremis presented to the emergency department with a severe asthma exacerbation and altered mental status. Dissociative state was achieved using aliquots of ketamine to facilitate NIPPV and medication administration. In less than 1 hour, the patient exhibited significant improvement and did not require intubation.

Although large studies on the benefits of NIPPV and ketamine in the setting of asthma are lacking, this case suggests that a strategy of subdissociative doses of ketamine with NIPPV could be considered as an initial step in the management of status asthmaticus before intubation.

Despite advances in outpatient treatment and an improved understanding of the pathophysiology, asthma continues to be a significant source of morbidity and mortality in the United States [1]. In 2007, there were 3447 deaths due to asthma; 3262 of those were among adults. Although there is certainly a component of chronic inflammation, the majority of the symptoms in acute asthma exacerbations can be reversed with proper medications and management [2]. Reversing bronchoconstriction and avoiding mechanical ventilation should be the goals of the emergency physician and the intensivist to avoid intubation and to view this intervention as a last resort.

The patient is a 36-year-old African American man who presented to our emergency department (ED) in severe respiratory distress. Per medics, the patient returned to his group home after taking a walk and developing severe dyspnea. By the time Emergency Medical Services arrived on scene, the patient was minimally responsive, was bradypneic, and had an initial pulse oximeter reading of 70%. An attempt at intubation was performed by the paramedic without medications. This attempt failed, as the stimulation of the laryngoscope caused the patient to gag and move.

On arrival to the ED, the patient’s history was limited given his clinical condition; but the patient had visited our ED 20 months prior and had a history of asthma and depressive psychosis. At that time, the patient had denied previous intubations but admitted to several previous hospitalizations without mention of intensive care unit–level care. Vital signs were rectal temperature of 35.1°C, heart rate of 124 beats per minute, respiratory rate of 26 breaths per minute, blood pressure of 147/87 mm Hg, and pulse oximetry of 98% on 10-L/min facemask with concurrent albuterol administration. Given his respiratory distress, a room air pulse oximeter reading was not obtained. On physical examination, the patient was sitting upright in a tripod position, perspiring profusely, and was unable to speak. His respiratory examination revealed markedly diminished breath sounds bilaterally, prolongation of the expiratory phase, and accessory muscle usage.

Immediately on arrival, the patient was started on nebulized albuterol and ipratropium. Throughout his ED stay, the patient was also given 125 mg methylprednisolone, 2 g magnesium sulfate, epinephrine 0.3 mg intramuscularly times 3 doses, and a 2000-mL bolus of isotonic sodium chloride solution. Within minutes, the decision was made to attempt bilevel positive airway pressure ventilation (BiPAP) given the patient’s altered mental status with potential for rapid deterioration and apnea. Just before BiPAP attempts, a point-of-care venous blood gas returned that showed a pH of 7.08, pCO2 of 67, and a lactic acid level of 79.0 mg/dL (8.769 mmol/L). A chest radiograph was obtained that showed hyperinflated lungs with no evidence of pneumothorax, pulmonary consolidation, or other etiology to explain the patient’s presentation.

Our initial attemps at BiPAP failed, as the patient would push away the respiratory therapist and was becoming increasingly agitated. Intubation equipment was brought to the bedside, and a 50-mg bolus of ketamine was given. The patient dissociated, and the BiPAP was applied with continuos albuterol solution flowing. After 10 minutes, an arterial blood gas (ABG) was drawn that showed a pH of 7.17, pCO2 of 63, and a PaO2 of 305 with an FIO2 of 100%. Several repeat boluses of 50 mg ketamine were given at approximately 5- to 10-minute intervals while the patient was on BiPAP to a total dose of 300 mg. After 40 minutes, an ABG showed a pH of 7.21, pCO2 of 59, and lactic acid level of 24.0 mg/dL (2.664 mmol/L). After this point, no further ketamine was needed because the patient was able to tolerate the BiPAP and participate in his care. At 120 minutes, his ABG showed a pH of 7.35 and pCO2 of 45. The patient was admitted to the medical intensive care unit on BiPAP, switched to nasal cannula, and discharged home from the general medical floor approximately 48 hours after his arrival to the ED in good condition.

Ketamine and noninvasive positive pressure ventilation (NIPPV) have both been proposed as adjunctive therapies for the management of severe asthma exacerbations. Though a 2012 Cochrane review found insufficient data to recommend NIPPV for status asthmaticus, this conclusion may be attributed to the lack of high-quality studies on the topic. Likewise, although ketamine exhibits physiologic effects that are beneficial in the setting of asthma [3–5] and there are case reports and small studies showing benefit [6–8], large randomized studies showing benefit are lacking.

In this case, the patient presented to us in a state that would have otherwise required mechanical ventilation. We believe that ketamine
and NIPPV provided time for our standard therapies to take effect, reverse the bronchoconstriction, and thereby avoid intubation. The patient had an uncomplicated hospital stay and was rapidly discharged, presumably because of the acute management. Further studies may help elucidate the role for these agents in the avoidance of mechanical ventilation in severe asthma exacerbations.

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http://dx.doi.org/10.1016/j.ajem.2015.03.066

References

Retrospective Analysis of Etomidate Versus Ketamine for First-pass Intubation Success in an Academic Emergency Department

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Abstract

Objectives: The objective of this study was to compare first-pass intubation success between patients who received etomidate versus ketamine for rapid sequence intubation (RSI) in the emergency department (ED).

Methods: This was a retrospective analysis of prospectively collected data recorded in a quality improvement database between July 1, 2007, and December 31, 2012. The study was conducted in an academic ED in the United States. All patients who received etomidate or ketamine as part of RSI were included. The primary outcome measure was first-pass success. A multivariate analysis was conducted to determine if sedative type was associated with first-pass success, after adjusting for potential confounders and baseline differences.

Results: The final cohort consisted of 2,098 RSI procedures using either etomidate (n = 1,983) or ketamine (n = 115). First-pass success occurred in 77.0% of patients in the etomidate group and 79.1% of patients in the ketamine group (difference = –2.1%; 95% CI = –5.5% to 9.8%). In the multivariate analysis, after adjusting for potential confounders, sedative type was not associated with first-pass success (odds ratio = 0.89; 95% CI = 0.5 to 1.5; p = 0.632).

Conclusions: Etomidate and ketamine are associated with equivalent first-pass success when used in RSI. Ketamine may be an appropriate alternative to etomidate for RSI in the ED.

Rapid sequence intubation (RSI) is the mainstay of airway management in critically ill emergency department (ED) patients. With the possible exception of patients who are unconscious and unresponsive, all patients needing RSI require the use of a sedative agent prior to neuromuscular blockade. The intent of the sedative is to render the patient unconscious and unaware, while the paralytic facilitates passage of the tracheal tube via muscular relaxation. Most studies evaluating intubation conditions or success rates have traditionally focused on comparisons of neuromuscular blockers. However, the sedative used may also influence intubating conditions and success rates by potentiating the effect of the neuromuscular blocker; reducing the time to maximal neuromuscular blockade; and affecting diaphragmatic, laryngeal, and pharyngeal reactivity to the intubation stimulus.

In previous systematic reviews and registry studies, the effect of the paralytic on intubation conditions was modified based on the sedative used. This suggests that sedative selection could also influence intubation success, which is a more clinically relevant outcome compared to intubation conditions. A previous study by Jabre et al., in which the primary focus was organ failure, reported intubation conditions and difficulty between etomidate and ketamine, but first-pass intubation success has not been evaluated as an outcome. The complications related to intubation (such as hypoxemia,
aspiration, bradycardia, and cardiac arrest) increase as the number of intubation attempts increase. Therefore, it is important that intubation success is achieved on the first-pass, and studies are needed to ascertain if ketamine use is associated with a reduction in intubation success compared to etomidate before it can be routinely recommended.

The primary goal of this study was to compare first-pass RSI success in ED patients who received etomidate versus ketamine. We hypothesized that there is no difference in first-pass success between the two agents.

**METHODS**

**Study Design**

This was retrospective analysis of prospectively collected data recorded in a quality improvement database between July 1, 2007, and December 31, 2012. The intent of the database is to evaluate resident performance, medications, and devices used for intubation in the ED. This study was granted exemption by the institutional review board.

**Study Setting and Population**

The study was performed in a 61-bed academic tertiary care ED with a census of approximately 75,000 patient-visits annually. Emergency physicians (EPs) primarily perform all intubations. During each intubation, physicians have access to a standardized intubation medication box containing the sedative etomidate, and the neuromuscular blockers succinylcholine, vecuronium, and rocuronium. Ketamine is available as an alternative agent via controlled access cabinets located in the ED. Sedative and neuromuscular blocker selection is primarily dependent on physician preference. All patients who underwent RSI in the ED were included. Patients were excluded if RSI was performed using a sedative other than etomidate or ketamine or if vecuronium was used for neuromuscular blockade instead of succinylcholine or rocuronium.

**Study Protocol**

The EP performing the intubation recorded data prospectively using a standardized data collection form, which was completed following the intubation. Pharmacy, billing, and admission records were used to identify any intubations performed without corresponding data forms, in which case the operators were contacted for form completion. Data collected included patient age, sex, trauma status (trauma or nontrauma), failure of prehospital intubation (failed or not attempted), presence of any difficult airway characteristics (blood or vomit in the airway, short neck, cervical collar, small mandible, obesity, airway edema, facial trauma, or large tongue), laryngoscopy device used, reason for device selection (standard, anticipate difficult airway, or educational reasons), reason for intubation (airway protection, respiratory failure, cardiac arrest, patient control, hypoxia), level of physician training (classified by postgraduate year [PGY] of residency training), medications used, and number of intubation attempts. The data were then entered into the electronic database program HanDBase 4.0 for the iPad (DDH Software, Wellington, FL) with subsequent transfer to Excel for Windows 2010 (Microsoft, Redmond, WA).

The primary outcome measure was first-pass success. The definitions of intubation attempt and intubation success were similar to those used in previous investigations. An intubation attempt was defined as the insertion and subsequent removal of the laryngoscopic device from the patient’s mouth, regardless of whether an attempt was made to pass a tracheal tube. Intubation success was defined as correct placement of the tracheal tube into the trachea, which was confirmed by end-tidal CO₂ capnometry, pulse oximetry, chest auscultation, observation of chest excursion, absence of epigastric sounds, and misting of the endotracheal tube.

**Data Analysis**

Patients were categorized into two groups based on the sedative used for intubation: etomidate or ketamine. Demographic and intubation data were compared between the two groups. An unpaired Student’s t-test was used to compare continuous, normally distributed variables. Normality was determined by visually inspecting the data. Fisher’s exact test was used to compare categorical variables. A multivariate logistic regression analysis was performed to determine the effect of sedative agent on first-pass success, after adjusting for confounders. Potential confounders that were included in the model were age, sex, paralytic used, trauma status, reason for intubation, device used, failure of prehospital intubation, reason for device selection, difficult airway parameters, and physician training. These were selected based on previous studies evaluating intubation success in this setting, and all variables were forced into the model. Age was categorized in the model as younger than 18, 18 to 65, and older than 65 years, since it did not meet the assumption of linearity in the log-odds. Difficult airway characteristics were entered into the model as ordinal variables. The model was checked for interactions and model fit was assessed by the Hosmer-Lemeshow goodness-of-fit test. No interactions were identified, allowing for all potential variables to be added in the same model. All statistical analyses were performed using Stata version 12 (StataCorp, College Station, TX) with significance for all analyses defined a priori as p < 0.05.

**RESULTS**

During the study period there were 2,258 RSIs performed in the ED. Of these, 113 were performed with sedatives other than etomidate or ketamine, 42 were performed with paralytics only, and five were performed with paralytics other than succinylcholine or rocuronium. Therefore, the final cohort consisted of 2,098 intubations using either etomidate (n = 1,983) or ketamine (n = 115). Overall, most intubations were performed by EPs (n = 2,019), followed by medical students or paramedics (n = 59) and physicians from other specialties (n = 20). The mean (±SD) patient age was 45.6 (±22.5) years, 63.5% of the patients were male, and the proportion of trauma patients was 44.0%. Comparison of baseline patient demographics and intubation
First-pass success occurred in 77.0% of patients in the etomidate group and 79.1% of patients in the ketamine group (difference = -2.1; 95% CI = -5.5 to 9.8). In the multivariate analysis, after the potential confounders and baseline differences were adjusted for, ketamine use was not associated with a reduction in first-pass success (odds ratio = 0.89; 95% CI = 0.5 to 1.5; p = 0.944). The data fit the model well (Hosmer-Lemeshow goodness-of-fit, p = 0.632) compared to etomidate. The data fit the model well (Hosmer-Lemeshow goodness-of-fit, p = 0.944).

**DISCUSSION**

First-pass intubation success is highly desirable because complications increase as the number of attempts increases. Previous studies have primarily focused on the effects of neuromuscular blockers, since they are directly responsible for muscular relaxation for passage of the tracheal tube. However, the sedative used can affect this outcome by a variety of potential mechanisms. For instance, the response to the intubation stimulus, such as diaphragmatic movement and coughing, can be influenced by the sedative used. Also, the onset time of neuromuscular blockade can be modified by the sedative. This is particularly important in the context of our study because ketamine has a longer onset of effect compared to etomidate. Therefore, if intubation is attempted prior to maximal neuromuscular blockade, intubation success could be affected.

Sivilliotti et al. evaluated the effect of a wide range of sedatives on intubation success in a multicenter observational study. They found that collectively, thiopental, methohexital, and propofol were associated with improved first-pass success, compared to other sedatives such as etomidate, ketamine, and benzodiazepines. They
hypothesized that the former group of sedatives produce a deeper plane of anesthesia, thereby facilitating intubation before complete neuromuscular blockade is achieved with paralytics alone. However, these former agents are seldom used for emergency intubation because of the potential for adverse effects such as hypotension. Our study builds on the results of Sivilotti et al. by focusing on etomidate and ketamine, two of the most commonly used sedatives for this indication due to their favorable hemodynamic profile. In addition, we included important confounders such as the intubation device used, which has recently been shown to be highly predictive of intubation success. Thus, our results are pertinent in an era in which video laryngoscopy is common.

In a recent randomized controlled trial by Jabre et al.7 655 patients who required emergency intubation were given either etomidate or ketamine for induction. There was no difference between groups with regard to the development of organ failure, which was the primary outcome. Although intubation success was not an outcome in this study, the difficulty of intubation was measured and was found to be comparable between the two groups. However, since this was not the focus of the study, important confounders were not measured. Our study is unique because we measured first-pass success, which was our primary outcome. We were unable to measure adverse effects, which is an important consideration in terms of sedative selection. However, the much larger study by Jabre et al.7 did not show differences in adverse effects, and these agents are considered to have similar safety profiles. Thus, given the fact that multiple intubation attempts are associated with an increase in adverse effects, we felt that first-pass success was the most important outcome to study.

LIMITATIONS

The study has a few limitations related to its design. The results should be extrapolated with caution to non-academic EDs. There is a possibility for measurement bias because physicians performing each intubation completed the data forms themselves. Ideally, an independent observer would collect this information. However, our main outcome variable was intubation attempts, and it is very unlikely that this variable would be erroneously documented. Some data collection forms were not completed immediately after the intubations and required the senior investigator (JCS) to contact individual physicians as part of a quality improvement process. Although this was done as quickly as possible, the delay in recording information in these cases could have led to recall bias. Nonetheless, the senior investigator verified information provided against medical records to ensure accuracy of documentation. It is possible that there was selection bias with regard to ketamine and etomidate. There were many more patients in the etomidate group, but we included all patients to minimize the potential for selection bias. Ideally, a randomized controlled trial would overcome this bias. However, we adjusted for differences between groups and performed the necessary model diagnostics. In addition, there could be individual variation between operators, but we could not stratify the results by operator because there were more than 150 operators in the database. Also, operator success could improve with number of previous intubations. Nonetheless, we included level of training as a surrogate for operator skill. We did not have dosing information of the paralytics, which could influence intubation conditions. There were several baseline differences between groups. However, we adjusted for this in our multivariate model. Finally, it is possible that there are additional confounders that were not included in our model. However, we have included the most likely variables, based on previous studies that could affect our outcome.

CONCLUSIONS

Etomidate and ketamine were associated with equivalent first-pass success in this retrospective review. A prospective randomized trial of first-pass success is needed to confirm these findings.

References

Study objective: We investigate a new technique for the emergency airway management of patients with altered mental status preventing adequate preoxygenation.

Methods: This was a prospective, observational, multicenter study of patients whose medical condition led them to impede optimal preintubation preparation because of delirium. A convenience sample of emergency department and ICU patients was enrolled. Patients received a dissociative dose of ketamine, allowing preoxygenation with high-flow nonrebreather mask or noninvasive positive pressure ventilation (NIPPV). After preoxygenation, patients were paralyzed and intubated. The primary outcome of this study was the difference in oxygen saturations after maximal attempts at preoxygenation before delayed sequence intubation compared with saturations just before intubation. Predetermined secondary outcomes and complications were also assessed.

Results: A total of 62 patients were enrolled: 19 patients required delayed sequence intubation to allow nonrebreather mask, 39 patients required it to allow NIPPV, and 4 patients required it for nasogastric tube placement. Saturations increased from a mean of 89.9% before delayed sequence intubation to 98.8% afterward, with an increase of 8.9% (95% confidence interval 6.4% to 10.9%). Thirty-two patients were in a predetermined group with high potential for critical desaturation (pre–delayed sequence intubation saturations ≤93%). All of these patients increased their saturations post–delayed sequence intubation; 29 (91%) of these patients increased their post–delayed sequence intubation saturations to greater than 93%. No complications were observed in the patients receiving delayed sequence intubation.

Conclusion: Delayed sequence intubation could offer an alternative to rapid sequence intubation in patients requiring emergency airway management who will not tolerate preoxygenation or peri-intubation procedures. It is essentially procedural sedation, with the procedure being preoxygenation. Delayed sequence intubation seems safe and effective for use in emergency airway management. [Ann Emerg Med. 2015;65:349-355.]

Please see page 350 for the Editor’s Capsule Summary of this article.

A podcast for this article is available at www.annemergmed.com.

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http://dx.doi.org/10.1016/j.annemergmed.2014.09.025

INTRODUCTION

Background

Preoxygenation and denitrogenation allow a safe buffer of oxygen to avoid hypoxemia during the apneic period of rapid sequence intubation. However, some patients struggle against traditional means of preoxygenation because of altered mental status. In these patients, we would be forced to proceed with rapid sequence intubation without the safety buffer of a large oxygen reservoir. Many of them will become hypoxemic during the apneic period and then require bag-valve-mask ventilation, with its attendant increased risks of gastric insufflation and aspiration.

In contrast to rapid sequence intubation, the technique of delayed sequence intubation temporally separates administration of the induction agent from the administration of the muscle relaxant to allow adequate preintubation preparation. The induction agent chosen is one that allows the continuation of spontaneous breathing and the retention of airway reflexes. The prototypical agent for this purpose is ketamine, a dissociative NMDA receptor antagonist. In the space of this separation, the patient can be preoxygenated and denitrogenated, and any necessary peri-intubation procedures can be performed. Only after completion of these crucial actions would the patient be paralyzed and intubated.

Importance

Patients who are intubated without adequate preoxygenation will have less apneic tolerance and are at risk for precipitous desaturation during intubation. If the patient’s preintubation oxygen saturation is less than or equal to 93%, he or she will likely continue to desaturate during the apneic period. Patients with inadequate preoxygenation and denitrogenation will have much shorter times until desaturation during intubation attempts. A technique to allow adequate preparation of delirious or combative patients for intubation could decrease the risk of hypoxemia and reduce peri-intubation morbidity and mortality.
Delayed Sequence Intubation

Editor’s Capsule Summary

What is already known on this topic
Adequate preoxygenation is difficult or even impossible in some patients with agitated delirium.

What question this study addressed
This small, observational study addresses whether a brief period of sedation with ketamine would improve ventilation and preoxygenation before intubation.

What this study adds to our knowledge
Postsedation oxygen saturations were successfully increased in the majority of patients.

How this is relevant to clinical practice
Delayed sequence intubation provides a feasible option for preoxygenation in the patient with altered mental status resistant to standard preoxygenation. Clinical outcomes were not assessed, and a randomized trial is warranted.

Goals of This Investigation
Our aim was to investigate the technique of delayed sequence intubation in a cohort of emergency department (ED) and critical care patients requiring emergency airway management in regard to improvement in preoxygenation and safety.

MATERIALS AND METHODS

Study Design
This was a prospective, observational study of patients whose medical condition or mental status led them to impede optimal preoxygenation, denitrogenation, or preintubation procedures. A convenience sample of patients was enrolled during the study period. Clinicians made attempts to preoxygenate and denitrogenate the study participants. If these patients did not allow the necessary preintubation preparations because of delirium, ketamine was administered until they became dissociated. At this point, preoxygenation and any necessary procedures were performed. After adequate preparation, in most cases the patients then received muscle relaxants and were intubated.

The study design complied with the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology statement. This study was approved by our institutional review board, as well as the Danish data protection agency; consent beyond what was standardly obtained for intubation was deemed unnecessary because delayed sequence intubation was considered usual care in these institutions.

Setting
The study was conducted at 3 institutions: a US 540-bed Level I trauma center, a US 1,100-bed quaternary referral center, and a Danish 1,200-bed Level I trauma center. This was primarily a study of ED patients; patients intubated in the ICU immediately on admission from the ED were also included at one of the study sites.

Selection of Participants
Patients included in this trial were undergoing emergency airway management. Patients were aged 18 years or older, spontaneously breathing, and not predicted by clinicians to have an anatomically difficult airway requiring awake intubation. Delayed sequence intubation was performed on patients who remained uncooperative after maximal attempts of traditional means of preoxygenation. Lack of cooperation included any of the following: verbal statements of inability to tolerate a mask or procedure, tearing off the mask, or inability to remain in the stretcher or bed. Attempts to perform preoxygenation included calm reassurance, help holding the mask, and explanations of the importance of preoxygenation. In most cases, delayed sequence intubation was performed after 3 attempts to facilitate standard preoxygenation.

Interventions
Patients undergoing delayed sequence intubation received titrated ketamine in a dose sufficient to achieve a dissociated state with continued spontaneously breathing and maintenance of airway reflexes (Figure 1). The recommended initial dose of ketamine was 1 mg/kg; additional aliquots of 0.5 mg/kg were administered until the patient was in a dissociated state.

Once the dissociated state was achieved, the patients were placed in an at least 30-degree head-up (semi-Fowler) positioning. They then received preoxygenation and denitrogenation with high-flow oxygen, using nonrebreather masks. If the nonrebreather mask was insufficient to raise the pulse oximeter saturation to greater than or equal to 95%, the patients began receiving noninvasive positive pressure ventilation (NIPPV), with continuous positive airway pressure settings of 5 to 15 cm H₂O, with no mandatory rate (spontaneous breath trigger). At this point, any procedures clinicians deemed necessary were performed, such as nasogastric tube placement.

After 3 minutes of denitrogenation, patients then received a muscle relaxant (succinylcholine or rocuronium) and began receiving nasal cannula aneic oxygenation, and intubation attempts were made 45 to 60 seconds afterward. In some cases, if the clinicians deemed the patient’s improvement after preoxygenation was so profound that intubation was no longer necessary, the procedure was delayed and the patient was allowed to emerge from dissociation. This was predicated on clinical judgment and not part of our delayed sequence intubation protocol. In these patients, the post–delayed sequence intubation oxygen saturation for the primary outcome was at 3 minutes after the administration of ketamine (the time muscle relaxants would have been administered).

Outcome Measures
The primary outcome of this study was the difference in oxygen saturations after maximal attempts at preoxygenation before delayed sequence intubation compared with saturations just before intubation. Maximal attempts at preoxygenation...
included attempting to verbally persuade the patient to keep on the oxygen mask or NIPPV mask or to allow the procedure and, if that failed, gently holding the mask on the patient’s face, without straps. The 2 points for the oxygen saturations were defined as the saturation just before the decision to proceed with ketamine administration (pre–delayed sequence intubation) compared with the oxygen saturation just before muscle relaxant administration (post–delayed sequence intubation). Predetermined secondary outcomes included the number of patients with pre–delayed sequence intubation saturations likely to progress to critical desaturation (SaO2 < 93%) and their post–delayed sequence intubation saturations, the number of successful nasogastric tube placements in patients who would not tolerate attempts at this procedure during their preintubation preparations, and the number of successful denitrogenations (defined as ≥3 minutes of tidal volume breathing while continuously exposed to a high-FiO2 source without any room-air breaths). Complications associated with delayed sequence intubation were tracked as well; the predetermined complications included pre–muscle relaxant apnea (defined as any apnea from 10 seconds after the administration of ketamine until the administration of muscle relaxant), peri-intubation emesis, and peri-intubation cardiac arrest or mortality (within 3 hours of intubation).

Primary Data Analysis
Descriptive statistics were assessed with means (SD). Mean differences between the saturations pre– and post–delayed sequence intubation were assessed with a paired t test because the data were normally distributed. Data were also analyzed with nonparametric methods (Wilcoxon signed rank test), with no difference in results. Computer analysis was performed with SPSS (version 22; IBM Corporation, Armonk, NY).

RESULTS
Sixty-four patients with delayed sequence intubation were included from May 2011 to December 2013 (Figure 2). Two patients were excluded because the pulse oximeter would not register post–delayed sequence intubation oxygen saturation. Both of these patients had arterial blood gases sent from their arterial lines at this point; the SaO2 values of these blood gases were both 100% and neither of these patients had any complications.
The Table summarizes the characteristics of the remaining 62 study patients. The mean patient age was 54 years; 33% were women. The Table also shows the patients’ underlying condition, the primary reason for intubation, and the reason delayed sequence intubation was needed. Fifty-five patients were intubated in an ED setting; 7, in an ICU. The mean total dose of ketamine administered to facilitate delayed sequence intubation was 112 mg. For the 42 patients with available weight data, the mean total dose was 1.4 mg/kg.

Saturations increased from a mean of 89.9% before delayed sequence intubation to 98.8% afterward, with an increase of 8.9% (95% confidence interval 6.4% to 10.9%). Figure 3 shows the saturation changes of the individual patients. Thirty-two patients were in the predetermined group with high potential for critical desaturation (pre–delayed sequence intubation saturations $\leq$ 93%). All of these patients increased their saturations post–delayed sequence intubation; 29 (91%) of them increased their post–delayed sequence intubation saturations to greater than 93%. All but 1 of these patients received NIPPV for preoxygenation during delayed sequence intubation.

Four patients with upper gastrointestinal bleeding received delayed sequence intubation to allow the placement of a nasogastric tube to drain their gastric blood before intubation; all 4 of these patients had successfully placed tubes confirmed by postintubation radiography. Of the 19 patients who received delayed sequence intubation to allow nonrebreather mask preoxygenation or denitrogenation, all were successfully denitrogenated for the 3-minute period.

Two patients were not intubated post–delayed sequence intubation. Both of them were asthmatic, with altered mental status. After administration of ketamine, both of these patients tolerated NIPPV. They received nebulized asthma medications and steroids. The clinicians deemed that the patients’ respiratory status improved sufficiently post–delayed sequence intubation that intubation could be avoided. Both of these patients emerged with continued improved respiratory status and were able to be admitted to the hospital, receiving NIPPV. They were subsequently discharged without the need for intubation.

No patients had pre–muscle relaxant apnea, peri-intubation emesis, cardiac arrest, or death. Two patients’ oxygen saturations decreased from the pre– to the post–delayed sequence intubation periods. The first patient’s saturation decreased from 99% to 98%; the second patient’s, from 95% to 93%. Both of these patients were receiving preoxygenation by nonrebreather masks without nasal cannula oxygen during their dissociation.

**LIMITATIONS**

This was not a randomized trial and therefore it is unknown what the patient outcomes would have been in these cases if
Table. Characteristics of study patients.

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<th>Characteristics</th>
<th>All Patients (N = 62)</th>
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<td>Age, mean, y</td>
<td>54</td>
</tr>
<tr>
<td>Range, y</td>
<td>18–79</td>
</tr>
<tr>
<td>Female, %</td>
<td>33</td>
</tr>
<tr>
<td>Location of intubation, Pts</td>
<td></td>
</tr>
<tr>
<td>ED</td>
<td>55</td>
</tr>
<tr>
<td>Critical care unit</td>
<td>7</td>
</tr>
<tr>
<td>Condition leading to need for intubation, Pts</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>20</td>
</tr>
<tr>
<td>Asthma</td>
<td>7</td>
</tr>
<tr>
<td>Acute pulmonary edema</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>Acute lung injury</td>
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<tr>
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<tr>
<td>Smoke inhalation</td>
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<tr>
<td>Sepsis encephalopathy</td>
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</tr>
<tr>
<td>Hepatic encephalopathy</td>
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<tr>
<td>UGIB</td>
<td>6</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>1</td>
</tr>
<tr>
<td>Trauma</td>
<td>2</td>
</tr>
<tr>
<td>Primary reason for intubation, Pts (%)</td>
<td></td>
</tr>
<tr>
<td>Oxygenation (type I) failure</td>
<td>42 (68)</td>
</tr>
<tr>
<td>Ventilatory (type II) failure</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Airway protection</td>
<td>18 (29)</td>
</tr>
<tr>
<td>Reason for DSI, Pts (%)</td>
<td></td>
</tr>
<tr>
<td>Intolerance of nonrebreather mask</td>
<td>19 (31)</td>
</tr>
<tr>
<td>Intolerance of NIPPV</td>
<td>39 (63)</td>
</tr>
<tr>
<td>Intolerance of nasogastric tube placement for UGIB</td>
<td>4 (6)</td>
</tr>
</tbody>
</table>

Pts, Patients; UGIB, upper gastrointestinal bleeding; DSI, delayed sequence intubation.

delayed sequence intubation had not been used. We collected patients as a convenience sample when the clinician deemed that delayed sequence intubation would have been beneficial; hence, there may be inherent selection bias. It is possible that a delayed sequence intubation was performed at one of these centers but the patient was not enrolled in the study. This is unlikely because all intubations were reviewed by a research associate specifically to screen for missed delayed sequence intubation.

All delayed sequence intubations were supervised by clinicians with extensive experience with ketamine sedation in adults; clinicians lacking familiarity with the medication may not have the same results. Furthermore, the study authors performed many of these intubations and may have given a higher level of care and attention because of a vested interest in good outcomes.

The study was small; there may be rare complications that will emerge only on the performance of larger trials, though a reassurance of safety can be extrapolated from the complication rate of ketamine for procedural sedation in adults. The safety of NIPPV in this cohort cannot be applied to all patients with altered mental status, such as obtunded or brain-injured patients. Although no patients in this cohort had tachycardia or hypertension necessitating treatment, these adverse events are potentially those of ketamine. Only adult patients were included; the safety and efficacy of delayed sequence intubation in the pediatric population is unknown, though there have been case reports of its use.8,9

DISCUSSION

In this prospective trial, we found that delayed sequence intubation allowed the provision of preoxygenation and denitrogenation to a patient population who would otherwise have been resistant to these important procedures. Traditionally, these patients would have proceeded directly to rapid sequence intubation, exposing them to the risks of peri-intubation bag-valve-mask ventilation such as gastric insufflation and aspiration. In patients with physiologic shunting, inadequate recruitment and preoxygenation can lead to severe hypoxemia and peri-intubation cardiac arrest. In this study, delayed sequence intubation was demonstrated to be effective and without observed complications in these patient groups during emergency airway management.

Delayed sequence intubation is often conflated with NIPPV preoxygenation. Although the 2 complement each other, delayed sequence intubation can be performed with standard preoxygenation as well. In this trial, 39 patients received preoxygenation with NIPPV; the remaining 23 patients achieved adequate preoxygenation and denitrogenation with nonrebreather mask alone.

There is a belief that NIPPV is contraindicated in patients with altered mental status. Although some ICUs have begun to challenge this prohibition in many classes of patients,10–12 the traditional reasons for the contraindication are not applicable to delayed sequence intubation. Ketamine-induced dissociation leads to the retention of airway reflexes and spontaneous breathing, in contrast to other causes of altered mental status.13 We believe this is a safe practice during the few minutes of preoxygenation as long as patients are carefully monitored by advanced airway practitioners throughout the delayed sequence intubation-preoxygenation.
In this study, a dose of 1 to 1.5 mg/kg was usually sufficient to dissociate patients requiring emergency airway management. Many of the complications of ketamine, such as hypersalivation, are dose dependent.\textsuperscript{13} Because ketamine will show its full clinical effects within seconds, it is logical to administer a smaller initial dose, such as 1 mg/kg, and then administer continued aliquots of 0.5 mg/kg until dissociation is achieved. In patients in whom immediate control is needed, a larger dose can be administered initially because even in 10-fold overdose spontaneous breathing and airway reflexes are retained.\textsuperscript{13}

In 2 of the delayed sequence intubations, the patients were judged by the clinicians to not require intubation after ketamine administration. Both of these were asthmatic patients who had significant improvement after beginning to receive NIPPV. Although this is not a recommended aspect of delayed sequence intubation, it bears future study. Other trials have examined the use of sedation to facilitate the provision of NIPPV.\textsuperscript{1,4} Ketamine may serve a similar role, but this trial is only suggestive of this possibility. If a clinician opts to attempt this technique, we recommend administering an anxiolytic such as ondansetron\textsuperscript{5} because, although peridissociation emesis from ketamine has not been reported in adults, postdissociation emesis is common.\textsuperscript{7} If such patients are allowed to emerge from sedation and are still in respiratory distress, they can be intubated with standard rapid sequence intubation technique because there will have already been an extensive period of preoxygenation.

The oxygen saturations of 2 of the patients minimally decreased while they were receiving denitrogenation. If during delayed sequence intubation there is a precipitous decrease in oxygen saturation, proceeding to standard rapid sequence intubation is likely the best course. These patients will likely be desaturating as a result of the continued effects of physiologic shunting, so a device incorporating positive end expiratory pressure should be used when reoxygenation of the patient is attempted (bag-valve-mask with positive end expiratory pressure valve, ventilator, etc.).\textsuperscript{1}

The trial researchers have explored the use of other agents to facilitate delayed sequence intubation, such as dexmedetomidine, droperidol, and remifentanil. However, they require further study before they can be recommended for this purpose. In contrast to ketamine, these agents require provision of an additional induction agent at administration of the muscle relaxant to ensure amnesia and adequate sedation. Some have suggested that standard induction agents such as etomidate or propofol or sedation agents such as midazolam could also be used for delayed sequence intubation. We strongly recommend against this because the nonapnea-inducing dosages of these agents may be very different in a patient requiring resuscitation than one receiving elective procedural sedation.\textsuperscript{4,6}

Delayed sequence intubation will not be commonly needed because most patients are able to tolerate peri-intubation preparation without additional sedation. Therefore, because it will not be performed often, if delayed sequence intubation is needed it is imperative to perform the procedure in a regimented fashion. All equipment for preoxygenation, intubation, and the possibility of difficult intubation should be at the bedside before ketamine administration. Medications for rapid sequence intubation should be drawn up and present at the bedside, including additional ketamine. A clinician should carefully observe the patient from the moment ketamine is administered until the endotracheal tube is placed and confirmed. Suction and ventilation devices should be prepared before the administration of ketamine.

Ketamine may cause a few seconds of transient apnea after initial rapid administration. Though ketamine-induced prolonged apnea has not been reported in the adult literature,\textsuperscript{6} we cannot exclude the possibility of this rare complication. In the event this occurs, we recommend the immediate administration of a muscle relaxant (succinylcholine or rocuronium), which will place the patient in the same situation as if standard rapid sequence intubation had been performed. A similar circumstance is ketamine-induced laryngospasm. Although relatively common in pediatrics, it has been reported only once in the adult cohort.\textsuperscript{7} Most situations of upper airway obstruction in adult ketamine dissociations are actually due to poor airway positioning, not laryngeal spasm. If actual laryngospasm occurs during delayed sequence intubation, the muscle relaxant should be administered, allowing standard rapid sequence intubation.

Additional information and media about delayed sequence intubation can be found at http://emcrit.org/dsi/.

Delayed sequence intubation could offer an alternative to rapid sequence intubation in patients requiring emergency airway management who will not tolerate preoxygenation or peri-intubation procedures. It is essentially procedural sedation, with the procedure being preoxygenation. Using this technique, a resuscitationist retains a higher degree of control when intubating a delirious patient. The traditional alternative is to progress to rapid sequence intubation without adequate preparation, which may result in morbidity. Randomized controlled trials of this technique would be welcome, but would be difficult, given this patient population. Delayed sequence intubation seems safe and effective for use in emergency airway management.

The authors acknowledge Alex Manini, MD, PhD, and David Shriger, MD, for their statistical advice and the FOAM community for encouragement and feedback.

Supervising editor: Gregory W. Hendey, MD

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Author contributions: SDW was responsible for the overall study and statistical review, was the principal investigator, collated...
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comments from other authors, prepared the final article, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. ST, JS, and NS were responsible for data collection. SDW and SSR were responsible for analysis and interpretation of the data and for study design. All authors critically reviewed the article. SDW takes responsibility for the paper as a whole.

Funding and support: By Annals policy, all authors are required to disclose any and all commercial, financial, and other relationships in any way related to the subject of this article as per ICMJE conflict of interest guidelines (see www.icmje.org). The authors have stated that no such relationships exist.

Publication dates: Received for publication August 7, 2014. Revision received September 16, 2014. Accepted for publication September 26, 2014. Available online October 23, 2014.

Presented as an abstract at the Society of Airway Management Scientific Assembly, September 2012, Toronto, Canada.

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Ketamine in refractory convulsive status epilepticus in children avoids endotracheal intubation

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ARTICLE INFO

Article history:
Revised 9 June 2015
Accepted 10 June 2015
Available online 16 July 2015

Keywords:
Ketamine
Status epilepticus
Refractory status epilepticus
Conventional anesthetics
Children
Endotracheal intubation

ABSTRACT

Objective: The purpose of this study was to report on the efficacy and safety of intravenous ketamine (KE) in refractory convulsive status epilepticus (RCSE) in children and highlight its advantages with particular reference to avoiding endotracheal intubation.

Methods: Since November 2009, we have used a protocol to treat RCSE including intravenous KE in all patients referred to the Neurology Unit of the Meyer Children’s Hospital.

Results: From November 2009 to February 2015, 13 children (7 females; age: 2 months–11 years and 5 months) received KE. Eight patients were treated once, two were treated twice, and the remaining three were treated 3 times during different RCSE episodes, for a total of 19 treatments. Most of the RCSE episodes were generalized (14/19). A malformation of cortical development was the most frequent etiology (4/13 children). Ketamine was administered from a minimum of 22 h to a maximum of 17 days, at doses ranging from 7 to 60 mcg/kg/min, obtaining a resolution of the RCSE in 14/19 episodes. Five patients received KE in lieu of conventional anesthetics, thus, avoiding endotracheal intubation. Ketamine was effective in 4 of them. Suppression-burst pattern was observed after the initial bolus of 3 mg/kg in the majority of the responder RCSE episodes (10/14).

Conclusions: Ketamine is effective in treating RCSE and represents a practical alternative to conventional anesthetics for the treatment of RCSE. Its use avoids the pitfalls and dangers of endotracheal intubation, which is known to worsen RCSE prognosis.

This article is part of a Special Issue entitled “Status Epilepticus”.

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1. Introduction

Status epilepticus (SE) is a life-threatening emergency traditionally defined as ‘an acute epileptic condition characterized by continuous seizures for at least 30 min, or by 30 min of intermittent seizures without full recovery of consciousness between seizures’ [1]. Convulsive SE is the most common and harmful form. Based on improved understanding of pathophysiology, there is now consensus that any seizure lasting longer than 5 min should be treated as SE [2].

Status epilepticus lasting longer than 120 min and not responding to first-line (benzodiazepines) and second-line (midazolam at a high dose, phenytoin, and phenobarbital) antiepileptic drugs (AEDs) is defined as “refractory” and requires Intensive Care Unit (ICU) treatment [3]. The term “super-refractory” defines SE that continues, or recurs, for 24 h or longer or recurs after withdrawal of anestheticpropofol infusion syndrome therapy [3]. Even with current best practice, neurological sequelae occur in >50% of children with refractory convulsive status epilepticus (RCSE) [4,5]. The mortality rate of RCSE ranges between 2.7 and 5.2% and increases up to 5–8% when only data from ICU are taken into account [4,5]. Refractory convulsive status epilepticus is generally treated with coma induction with high-dose midazolam or thiopental or propofol [6–8]. However, the high risk of “propofol infusion syndrome” often limits its use in children [9].

Increasing evidence indicates that ketamine (KE), a potent N-methyl-D-aspartate antagonist, may be effective in treating RCSE [10]. Compared to conventional anesthetics, KE has neither cardiac nor respiratory depressant properties. Its administration, therefore, does not imply emergent endotracheal intubation, a prognostic factor of increased morbidity and mortality risk in critically ill adults and children [11–13].

Here, we report our experience using KE in a treatment protocol for children with RCSE, extending our initial series of patients [14] and including those children in whom KE was administered prior to conventional anesthetics.

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1 These authors contributed equally to the manuscript.
2. Material and methods

Since November 2009, our Pediatric Neurology Unit at the Meyer Children's Hospital (Florence, Italy) has used a treatment protocol for RCSE including intravenous KE infusion. S(+)-ketamine (Ketanest S®; Parke-Davis, Freiburg, Germany) was the isof orm we used until November 2011. We subsequently started using racemic KE (Ketamina®, Molteni S.p.A., Italy) as the only form of the drug available at our hospital.

Since January 2013, to avoid mechanical ventilation, we have used KE (Ketamina®, Molteni S.p.A., Italy) before considering conventional anesthetics. We have set as primary endpoint the control of both electrical and clinical seizures under continuous video-EEG recording.

By protocol, we administer 2 boluses of 2–3 mg/kg each of KE 5 min apart, immediately followed by continuous infusion of 5–10 mcg/kg/min. Based on both the clinical and electrographic response, we then increase the dose every 10 min or longer, using 2 to 10 mcg/kg/min increments, up to 60 mcg/kg/min [14]. We administer add-on midazolam at 1 mcg/kg/min to prevent emergent side effects such as hallucinations. Routine blood tests are performed regularly.

We collected clinical and EEG features of all patients treated with KE, including age at diagnosis, sex, type of SE, etiology, age at onset and duration of SE, type and doses of additional AEDs and conventional anesthetics (when applicable), sequence of drug administration, tolerability, and outcome.

The pediatric ethics committee of the Tuscany region approved the study. Written informed consent of the parents was required before KE administration.

3. Results

Between November 2009 and February 2015, 68 consecutive patients were admitted for SE, and 29 of them were transferred to the ICU because of RCSE. Thirteen children (7 female) received intravenous KE. Eight patients were treated once, two were treated twice, and the remaining three were treated 3 times during different RCSE episodes, for a total of 19 treatments (Table 1). Ten RCSE episodes were treated with S(+)-ketamine, while racemic KE was administered in the remaining 9. Patients' ages at the time of treatment ranged from 2 months to 11 years and 5 months (mean: 5 years and 3 months; median: 3 years and 4 months).

A history of epilepsy preceding RCSE was present in 11 patients; SE had previously occurred in 7. Most of the RCSEs were generalized (14/19), and the most frequent etiology was a cerebral malformation (4/13 children).

The initial therapy for SE was started within a median of 15 min from admission (range: 10–45 min). Ketamine was applied within a median time of 7 days (range: 5 h–26 days). The median KE dose was 30 mcg/kg/min (mean: 33.6 ± 4.5 mcg/kg/min; range: 7–60 mcg/kg/min). In 14/19 treatments, KE was administered after conventional intravenous anesthetics: midazolam, 8 pts (mean: 3.2 ± 1.9 mcg/kg/min; median: 3 mcg/kg/min); propofol, 4 pts (mean: 4.1 ± 1.8 mcg/kg/h; median: 4.5 mcg/kg/h); thiopental, 4 pts (mean: 7.8 ± 3.7 mcg/kg/h; median: 9 mcg/kg/h). Median duration of KE administration was 3 days (mean: 4.2 ± 1.9 days; range: 1–17 days).

The use of KE was associated with resolution of RCSE in 14 episodes; a burst suppression EEG pattern was obtained in 10. In the remaining 4 episodes, resolution of the RCSE was obtained through the appearance of delta activity and a rapid, progressive reduction in seizure frequency (maximum: 8 per day).

In 5 children (2 females; age range: 4 months–11 years and 5 months), KE was administered in lieu of conventional anesthetics, thus, avoiding mechanical ventilation. In all of them, the maximum dose infusion was 60 mcg/kg/min (range: 7–60 mcg/kg/min; median: 20 mcg/kg/min) for a maximum of 4 days (range: 1–4 days, median: 2 days). Status epilepticus control was obtained in 4/5 individuals. The only nonresponder was completely seizure-free for 8 h with 20 mcg/kg/min of KE, yet, daily seizures recurred during and after the drug withdrawal.

Among the 19 RCSE episodes, 5 were not controlled by KE. In 2 of the 5 no responders, SE, which became eventually life-threatening, was successfully treated by surgical removal of focal cortical dysplasia.

During KE administration, a slight increase of saliva production occurred in all patients. A transient, mild increase of liver enzymes

### Table 1

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex</th>
<th>Age</th>
<th>Neurological examination</th>
<th>Diagnosis</th>
<th>Etiology</th>
<th>Seizure types during SE</th>
<th>KE dosage (mcg/kg/min)</th>
<th>EEG after iv. KE</th>
<th>KE efficacy</th>
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</thead>
<tbody>
<tr>
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</tr>
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<tr>
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<td>FE</td>
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<td>11 years and 5 months</td>
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<td>FE</td>
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<tr>
<td>12d</td>
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<td>3 years and 3 months</td>
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<td>EE</td>
<td>Malformative</td>
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<td>Unknown</td>
<td>Focal, My</td>
<td>20</td>
<td>BS</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Legend: BS, burst suppression pattern; CI, cognitive impairment; EE, epileptic encephalopathy; F, female; FCD, focal cortical dysplasia; FE, focal epilepsy; FIES, febrile infection-related epilepsy syndrome; GC, generalized convulsive; iv., intravenous; KE, ketamine; M, male; MELAS, Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; My, myoclonus; SE, status epilepticus; SG, secondary generalization.

- First treatment with ketamine.
- Second treatment with ketamine.
- Third treatment with ketamine.
- Cases treated with KE without endotracheal intubation.
occurred in 4 children who had also received phenobarbital. No additional adverse events were observed, in particular, no psychotomimetic changes, respiratory depression, or hemorrhagic cysts occurred.

Follow-up brain MRI was performed 3 to 12 months (median: 6.5 months) after KE treatment in 6 patients. Two patients, both with an unknown progressive disorder, exhibited worsening of preexisting brain atrophy, which we attributed to the underlying condition; 2 patients with febrile infection-related epilepsy syndrome (FIRES) exhibited mild atrophic changes, a likely consequence of the causative encephalopathy; and no change occurred in the remaining 2 patients.

4. Discussion

Our series (Class IV of evidence), although small, provides further evidence of the efficacy of KE for treating RCSE in children and its safety profile [14]. Status epilepticus resolution was obtained in 14/19 RCSE episodes, and none of the 13 patients experienced serious adverse events. In 2 of the 5 RCSE episodes in which the drug was ineffective, resolution of the SE, even after the failure of conventional anesthetics, was obtained only with surgical treatment. Ketamine was also effective in 4/5 children that received it prior to conventional anesthetics, thus, avoiding the risks of endotracheal intubation in the management of RCSE. Thus, we believe that KE therapy should be considered before conventional anesthetics in the treatment algorithms of RCSE.

Status epilepticus is a significant cause of morbidity and mortality in the pediatric population [4,5]. Management of SE includes systemic support of airway and circulation, seizure control, prevention of recurrence, and treatment of the underlying cause. The underlying etiology is the main determinant factor of mortality [4], whereas the main cause of death is an acute respiratory distress syndrome, which is regarded as either the result of prolonged and continuous infusion of high-dose anesthetics or the complication of the late phase of RCSE [11,13].

There are a general consensus over the first and second lines of treatment of SE. Although the types of drugs are similar in different countries, the algorithm/protocols may differ, as well as between institutions. Conversely, there is currently no definitive data or consensus to guide both the optimal choice of therapy and treatment goals for RCSE [3,6–8]. Refractory convulsive status epilepticus is generally treated with coma induction using high-dose midazolam or conventional anesthetics such as thiopental or propofol [6,8], although the high risk of propofol infusion syndrome is often a limitation to the use of this drug in children [9]. While conventional anesthetics are effective, their intravenous administration is associated with hypotension, myocardial depression, and low cardiac output that require ICU admission. All these drugs also require endotracheal intubation, which represents a negative prognostic factor of morbidity and mortality [11–13].

Between 15 and 39% of emergent endotracheal intubations in adults are associated with one or more complications, including severe hypoxemia, hemodynamic collapse, and death [11,13]. In the pediatric population, the complication rate is even higher, and acute deterioration can occur rapidly as a result of age-related differences in physiology, oxymoglobin dissociation, oxygen consumption, and pulmonary mechanics [12].

Because of its sympathomimetic action, KE has no cardiac depressant properties and does not cause hypotension [15]. Owing to its pharmacological properties, KE use does not necessarily require amine administration or mechanical ventilation. Large doses of KE and rapid intravenous boluses may cause hallucinations, which are less frequent in children than in adults and can be reduced with benzodiazepine premedication [15]. Ketamine has neuroprotective properties by preventing transduction of signals to destructive intracellular mechanisms through the blocking of NMDA receptors [15,16].

Differences between the drug’s two isomers have been reported with regard to their anesthetic potency and EEG effects [17,18]. In our series, response-adjusted dosage did not result in different dosages of the two drug preparations, in different rates of adverse events or types of EEG patterns.

Experimental models suggest that, with continuing seizures, inhibitory y-aminobutyric acid (GABA_A) receptors are internalized in clathrin-coated vesicles, and excitatory N-methyl-D-aspartate (NMDA) receptors are mobilized to the membrane [19,20]. This receptor-trafficking results in decreased inhibitory control and increased excitation that may foster sustained SE [19,20]. Conventional anesthetics, which all act on GABA_A receptors, will, therefore, be less active, making higher doses necessary, which will in turn enhance their untoward effects, especially hypotension, and, thus, require vasopressor administration [13]. In this scenario, NMDA modulating molecules such as KE represent an attractive alternative in status epilepticus [10]. The literature has provided good evidence for the potential benefit and low adverse events of KE, in both the adult and pediatric populations with RCSE. However, the heterogeneity of prior treatments, time to KE administration (which is always considered after conventional anesthetic failure), and KE dosage and duration make available information on seizure responsiveness difficult to interpret.

Our pediatric series shows that treatment with KE in RCSE is effective and safe, and its use should be considered before thiopental and propofol, unless specific contraindications to KE exist. Based on these encouraging results, we have designed a national multicenter randomized sequential trial, which has been approved by the Italian Medicines Agency and includes ten pediatric hospitals (EudraCT number 2013–004396–12; ClinicalTrials.gov identification number: NCT02431663).

Acknowledgments

We would like to thank Debora Di Maina, Elisa Nacci, and the team of EEG technicians of the Neurophysiology Laboratory for their technical support, especially concerning the extensive data acquisition and handling.

Conflict of interest

The authors have stated that they had no interests that might be perceived as posing a conflict or bias.

References


KETAMINE USE FOR ACUTE AGITATION IN THE EMERGENCY DEPARTMENT

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Abstract—Background: Emergency physicians regularly encounter agitated patients. In extremely agitated and violent patients, the onset of many traditional medications is relatively slow and often requires additional medication. Ketamine is frequently used in emergency departments (EDs) for procedural sedation and intubation, but has recently been suggested as a treatment for acute agitation.

Objectives: We sought to examine the use of ketamine in the treatment of acute agitation in an ED setting, including vital sign changes as a result of this medication.

Methods: This is a structured review of an historical cohort of patients over 7 years at two university EDs. Patients were included if they received ketamine as treatment for acute agitation. Abstracted data included age, vital signs including hypoxia, any additional medications for agitation, and alcohol/drug intoxication.

Results: Ketamine was administered for agitation on 32 visits involving 27 patients. Preadministration systolic blood pressure was 131 ± 20 mm Hg, with an average postadministration increase of 17 ± 25 mm Hg. The average baseline heart rate was 98 ± 23 beats/min, with an average increase of 8 ± 17 beats/min. No patients became hypoxic; 62.5% of patients required additional calming medication. Alcohol or drug intoxication was present in 40.6% of patients.

Conclusions: We found ketamine was used rarely, but had few major adverse effects on vital signs even in a population with 21.9% alcohol intoxication. However, a high proportion (62.5%) of patients required additional pharmacologic treatment for agitation, implying that administering ketamine is useful only for initial control of severe agitation.

Keywords—ketamine; agitation; aggression; control; vital signs

INTRODUCTION

Emergency physicians regularly encounter agitated patients in the emergency department (ED) (1–11). Causes of ED-based agitation are numerous, ranging from psychosis to intoxication (2–5,8). Although verbal de-escalation is recommended as first-line treatment, in some cases this can be ineffective and medication administration may be required to prevent these patients from harming themselves or others (10,12). However, many of these medications have a relatively slow onset, require empiric dosing, and often require additional medication for calming (10,13).

Ketamine is a dissociative agent acting through antagonism of glutamate N-methyl-D-aspartate receptors, which causes a trance-like state resulting in analgesia and amnesia (14). It is frequently used in EDs for procedural sedation as well as an induction agent for intubation, but has only recently been proposed as a treatment for agitation. Dissociative anesthesia occurs in 1–2 min...
The purpose of this study is to examine the efficacy and safety of ketamine in the treatment of acute agitation in an ED setting. Given a recent report that ketamine use in the prehospital setting was associated with a surprising number of oxygen desaturations, the primary measurement of interest was any increases or decreases in vital signs after ketamine, particularly oxygen saturation (21).

**Objectives**

The purpose of this study is to examine the efficacy and safety of ketamine in the treatment of acute agitation in an ED setting. Given a recent report that ketamine use in the prehospital setting was associated with a surprising number of oxygen desaturations, the primary measurement of interest was any increases or decreases in vital signs after ketamine, particularly oxygen saturation (21).

**Materials and Methods**

**Study Design and Setting**

This is an historical cohort study at two university EDs, one urban academic teaching hospital, and one suburban community hospital. Combined, these EDs treat approximately 65,000 patients per year. This study was approved by the local institutional review board prior to data collection.

**Selection of Participants**

The cohort was identified by a keyword search of the electronic medical record (EMR) for all patients who received ketamine between September 15, 2004 and June 6, 2012. Patients were included if ketamine was administered as treatment for acute agitation. Agitation was defined, following recent American Association for Emergency Psychiatry BETA project guidelines, as “an extreme form of arousal that is associated with increased verbal and motor activity” (25). This definition was operationally adapted for use by including situations where the patient was noted to be physically aggressive with staff, require restraints, or have increased verbal/motor activity interfering with treatment. Patients were excluded if they received ketamine for any other reason, including procedural sedation or intubation, or if the chart was irretrievable.

The following variables were queried from the EMR: age, sex, and chief complaint. The following data were then abstracted by blinded research associates: patient vital signs (heart rate, blood pressure, respiratory rate, and oxygen saturation), route/dose/time of ketamine administration, peak blood levels of ketamine, additional calming medication within 3 h, alcohol levels measured via serum alcohol/breathalyzer, and urine toxicology lab results when available. If available, preadministration vital signs were recorded as close to the initial administration of ketamine as possible. If available, postadministration vitals were recorded for both the lowest and highest values of a particular vital sign parameter that were recorded within 4 h of administration. Additional calming medication was defined as additional antipsychotics, benzodiazepines, or ketamine administered for agitation within 3 h of the initial dose of ketamine. Although 3 h is not based on the half-life of ketamine, this figure has been used in other agitation investigations of this type (26–29). All records were evaluated by a minimum of three researchers who were trained on use of the EMR. At least 2 research assistants evaluated the EMR for each patient visit and selected those cases where ketamine was given for agitation; once all researchers had completed their review, the results were compared. Full consensus between the researchers was required for inclusion. Patients selected for inclusion subsequently had their EMR further evaluated for return to the ED for exacerbation of any psychiatric issues after administration of ketamine.

**Data Collection and Processing**

All data were entered into a standardized computer worksheet using Excel 2010 (Microsoft, Redmond, WA), and then checked for nonsensical values. Change in vital signs within 4 h after administration of ketamine was calculated...
relative to the baseline vital sign preadministration within each patient to prevent small changes in baseline vital signs from skewing the analysis across patients. Four hours postmedication administration was chosen, as this has been used in other investigations of this type and is approximately equal to two half-lives of ketamine ($t_{1/2} = 2.17$ h) (23,26–29). Hypoxia after administration of ketamine was defined as an oxygen saturation of $<90\%$.

**Outcome Measures**

The primary outcome measures were change in vital signs postadministration and the need for any additional calming medication. Vital sign changes were calculated within a particular patient, as noted above.

**Primary Data Analysis**

Descriptive statistics were used to evaluate patient characteristics such as age, gender, change in vitals, ketamine dose, and proportions of patients who received additional calming medication within 3 h.

**RESULTS**

Over the study period, 459 patients who received ketamine in the ED were identified. Thirty-two cases involving 27 patients met study inclusion and exclusion criteria and were subjected to further analysis. The remaining 427 patient visits received ketamine for non-agitation-related causes, primarily for procedural sedation or induction of intubation. One autistic, nonverbal patient who was uncooperative with treatment received ketamine on five separate visits. The age range of the study group was from 9 to 77 years (average age of 35 ± 16 years; 20 males). Weight was recorded in five patient visits. Discharge diagnoses, age, and gender for each patient are listed in Table 1.

A total of 17 patient visits received intramuscular (i.m.) ketamine, and 15 received intravenous (i.v.) administration. In 18 (56.2%) cases, a patient received medication for agitation prior to being administered ketamine, most often a combination of an antipsychotic and a benzodiazepine. On 20 patient visits (62.5%), additional calming medication was utilized, most often additional ketamine. In eight (25%) visits, both pre- and postadministration medication was required. Thirteen patients intoxicated with alcohol or other substances (40.6%) required additional calming medication at a higher rate than those who were not (84.6% vs. 47.4%). A summary of medication and intoxication can be found in Table 2. In no cases were dysphoric emergence reactions noted, and in no cases did patients return to the ED for noted exacerbations of psychiatric conditions due to ketamine.

| Case | Gender | Age, Years | Discharge Diagnosis*
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>10</td>
<td>Agitation (autism/tuberous sclerosis)</td>
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<tr>
<td>2</td>
<td>F</td>
<td>9</td>
<td>Head trauma</td>
</tr>
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<td>3</td>
<td>M</td>
<td>36</td>
<td>Alcohol intoxication</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>31</td>
<td>Polysubstance intoxication</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>20</td>
<td>Leg pain (autism)</td>
</tr>
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<td>6</td>
<td>M</td>
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<tr>
<td>7†</td>
<td>F</td>
<td>24</td>
<td>Ovarian cyst (autism)</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>40</td>
<td>Primary psychosis &amp; polysubstance intoxication</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>41</td>
<td>Polysubstance intoxication</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>28</td>
<td>Amphetamine intoxication</td>
</tr>
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<td>11†</td>
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<td>M</td>
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<td>Head trauma (developmental delay)</td>
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<td>18</td>
<td>M</td>
<td>53</td>
<td>Amphetamine intoxication</td>
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<td>F</td>
<td>30</td>
<td>Suicide attempt</td>
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<td>F</td>
<td>40</td>
<td>Chronic pain</td>
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<td>F</td>
<td>19</td>
<td>Polysubstance intoxication</td>
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<td>12</td>
<td>Antipsychotic medication change (autism)</td>
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<td>77</td>
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<td>M</td>
<td>53</td>
<td>Primary psychosis &amp; cocaine intoxication</td>
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<td>Primary psychosis &amp; alcohol intoxication</td>
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<td>M</td>
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<td>Alcohol intoxication</td>
</tr>
<tr>
<td>31</td>
<td>F</td>
<td>71</td>
<td>Dementia</td>
</tr>
<tr>
<td>32</td>
<td>M</td>
<td>47</td>
<td>Alcohol intoxication</td>
</tr>
</tbody>
</table>

* Parentheses after the diagnosis contains conditions indicated to be exacerbating agitation or impeding treatment.
† These five cases represent the same patient on different visits to the emergency department.

There were sufficient data to evaluate postadministration change in systolic blood pressure (SBP) in 22 visits with an average predadministration SBP of 131 ± 20 mm Hg. Within 4 h of administration, the highest recorded SBP for each patient showed an average increase of 17 ± 25 mm Hg from the patient’s baseline. The lowest recorded SBP in the same time period showed an average drop of 14 ± 24 mm Hg. Change in heart rate was evaluated in 25 cases; the average predadministration heart rate was 98 ± 23 beats/min. The average highest increase from baseline was 8 ± 17 beats/min, and the largest decrease was 10 ± 18 beats/min. Twenty-two cases provided oxygen saturation data in which the predadministration average was 98 ± 2%. Postadministration average highest increase was 1.1 ± 1.7%, and average largest decrease was 0.6 ± 2.2%. No patients became hypoxic; the lowest oxygen saturation after administration was 94%. A summary of change in SBP and heart rate can be found in Table 3.
<table>
<thead>
<tr>
<th>Case</th>
<th>Prior Medication</th>
<th>Initial Ketamine Dose</th>
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<td>1</td>
<td></td>
<td>150 mg i.m.</td>
<td>+00:50 Ketamine 150 mg i.m.</td>
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</tr>
<tr>
<td>2</td>
<td></td>
<td>40 mg i.m.</td>
<td>+00:13 Ketamine 40 mg i.m.</td>
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<tr>
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<td></td>
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<tr>
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<td></td>
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<td></td>
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<td>+01:02 Midazolam 2 mg i.m.</td>
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</tr>
<tr>
<td>3</td>
<td></td>
<td>200 mg i.m.</td>
<td>+00:35 Ketamine 200 mg i.m.</td>
<td></td>
</tr>
<tr>
<td>4</td>
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<td>160 mg i.v.</td>
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<td>Lorazepam 2 mg i.m.</td>
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<td>+00:17 Lorazepam 2 mg i.m.</td>
<td>BAL 119 mg/dL</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>+01:25 Ketamine 100 mg i.m.</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+02:50 Ketamine 200 mg i.m.</td>
<td>&quot;Mushrooms&quot;</td>
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<td>6</td>
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<td>+00:10 Ketamine 100 mg i.m.</td>
<td>&quot;Alcohol&quot;</td>
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<td>&quot;Cocaine&quot;</td>
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<td></td>
<td>+02:50 Ketamine 200 mg i.m.</td>
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<tr>
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<td>&quot;Methamphetamine&quot;</td>
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<td>+00:20 Lorazepam 2 mg i.v.</td>
<td>&quot;Methamphetamine&quot;</td>
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</tr>
<tr>
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</tr>
<tr>
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<td>100 mg i.v.</td>
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<td>&quot;Methamphetamine&quot;</td>
</tr>
<tr>
<td>27</td>
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<tr>
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<td>+00:20 Lorazepam 2 mg i.v.</td>
<td>&quot;Methamphetamine&quot;</td>
</tr>
</tbody>
</table>

(Continued)
DISCUSSION

Several case reports have documented the potential usefulness of ketamine in severe agitation (13,21,30,31). The putative advantages of this medication for agitation include rapid onset, the preservation of airway reflexes, and the ability to administer either i.m. or i.v., which may itself be particularly useful if i.v. access is not easily obtained. In addition, sedation is often achieved reliably with one dose(23). Compared to other agents, the half-life of ketamine is relatively short, potentially allowing more rapid disposition of agitated patients (23).

### Table 2. Continued

<table>
<thead>
<tr>
<th>Case</th>
<th>Prior Medication</th>
<th>Initial Ketamine Dose</th>
<th>Additional Medical Intervention</th>
<th>Intoxication†</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td></td>
<td>160 mg i.m.</td>
<td>+00:41 Ketamine 240 mg i.m.</td>
<td>BAL 079 mg/dL</td>
</tr>
<tr>
<td>30</td>
<td></td>
<td>150 mg i.m.</td>
<td>+01:29 Droperidol 1.25 mg i.v.</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>–01:56 Haloperidol 5 mg i.m.</td>
<td>40 mg i.v.</td>
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<td>+01:56 Lorazepam 2 mg i.v.</td>
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<td></td>
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</tr>
<tr>
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<td></td>
<td>+01:56 Lorazepam 2 mg i.v.</td>
<td></td>
</tr>
</tbody>
</table>

BAL = blood alcohol level.

"-" and "+" for prior medication and additional medical intervention indicate time in relation to initial ketamine dose.

Quotation marks indicate physician-reported patient use/intoxication.

* Medication reported to be given shortly prior to arrival. Time indicated is triage time in relation to ketamine administration time.

† Clonazepam dose not indicated.

### Table 3. Patient Vitals Pre- and Postadministration of Ketamine

<table>
<thead>
<tr>
<th>Case</th>
<th>Ketamine Dose (mg)</th>
<th>Systolic Blood Pressure (mm Hg)</th>
<th>Heart Rate (Beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Predose</td>
<td>Postdose (High)</td>
</tr>
<tr>
<td>1</td>
<td>150</td>
<td>86</td>
<td>104</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>93</td>
<td>102</td>
</tr>
<tr>
<td>5</td>
<td>400</td>
<td>121</td>
<td>115</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>109</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>320</td>
<td>119</td>
<td>107</td>
</tr>
<tr>
<td>9</td>
<td>140</td>
<td>75</td>
<td>64</td>
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<tr>
<td>11</td>
<td>200</td>
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<td>32</td>
<td>144</td>
<td>94</td>
<td>99</td>
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</tbody>
</table>

Postdose vitals contain highest and lowest recorded values within 4 h of ketamine administration. Cases where vitals were not charted are not included; blank spaces are indicative of that vital not being charted in that specific case.
Potential disadvantages of ketamine include the fact that patients who are in a dissociative state are unable to participate in their own care (4,5,10). Ketamine also does not treat the underlying cause of agitation, and if the etiology of the agitation persists, patients may require multiple doses of additional calming medications. In this study, for instance, patients with substance/alcohol intoxication needed calming medication at higher rates. Finally, there is evidence from at least one double-blind placebo-controlled trial that subanesthetic doses of ketamine may worsen psychosis, which may make use of this medication inappropriate in patients who have a psychiatric cause of their illness (32).

Little has been published on the use of ketamine for agitation. Roberts & Geeting described in a case study the successful treatment of an acutely agitated and violent patient with i.m. ketamine without major adverse effects, and a case series by Le Cong et al. reported that ketamine provided adequate sedation in agitated psychiatric patients who had not responded to treatment with benzodiazepines, without any major adverse effects (13,30). However, these report did not follow long term to confirm any worsening of psychosis after administration.

Much of the ED literature has focused on changes in vital signs. Burnett et al. report on several patients administered ketamine in the prehospital setting who had surprising decreases in oxygen saturations (21). In terms of other vital sign parameters, increases in blood pressure and heart rate are frequently seen, but are rarely clinically significant (15). This is true in the study above as well, in which increases in blood pressure and heart rate are frequently present but not noted as significant. In four cases, the highest recorded blood pressure after ketamine administration was lower than the predose SBP; this trend was also seen in heart rate in eight cases. In these cases, the effect of calming during an agitated episode on vitals may outweigh any changes induced by ketamine. Additionally, in no cases were significant changes in oxygen saturation noted, and no patients became hypoxic, contrary to the results seen in prehospital literature.

Slightly over half of the cases (62.5%) required additional medication for agitation after receiving ketamine, suggesting ketamine alone in the dose used is often not enough to resolve agitation. This is not unexpected as typically, ketamine was being used to gain rapid and safe control of severely agitated patients to facilitate a more structured medical evaluation. As ketamine has not been proposed specifically as a treatment for agitation from undertreated psychiatric illnesses or even sympathomimetic drug intoxication, but rather as a means to permit initial work-up of an agitated patient, it is perhaps not surprising to find that the majority of patients required additional medications.

Of interest, there were eight cases (Table 2: patients 14, 15, 16, 18, 19, 20, 24, and 25) where multiple doses of an antipsychotic or a benzodiazepine were given without resolution of agitation. Once given ketamine, these patients either did not require additional calming medication at all or did not need it within 3 h. Two of these patients, 18 and 19, received a “B-52” consisting of haloperidol, lorazepam, and diphenhydramine, traditionally thought to be extremely effective in sedating agitated patients, yet still required ketamine to resolve agitation. This may highlight ketamine’s usefulness with severely agitated patients, as well as introducing ketamine as a potential alternate medication for patients nonresponsive to traditional pharmacological interventions.

Limitations

The retrospective, case series nature of this study may suffer from selection bias, as patients were not prospectively randomized and enrolled in treatment arms. The small patient population of the study also limits the ability to generalize to other populations. Incomplete charting led to a lack of vitals for several of the patients, decreasing our ability to further evaluate ketamine’s reported effects on vital signs. A patient’s weight is not routinely included in ED charts, and so precludes further evaluation of the appropriateness of dosing in most cases.

CONCLUSIONS

Relative to other pharmacologic treatments for agitation, ketamine is infrequently used in the ED. We found that ketamine was used without any major adverse effects on vital signs, even in a population with 21.9% alcohol intoxication. However, a high proportion (62.5%) of patients required additional pharmacologic treatment for their agitation, implying that ketamine itself is not an ideal treatment for the underlying cause of agitation, but rather a means of initial management of severe agitation. A prospective study is warranted to further clarify the safety and efficacy of the use of ketamine in this situation.

Acknowledgments—Portions of these data were presented at the National Update on Behavioral Emergencies conference, Orlando, Florida, 2013.

REFERENCES

6. Campillo A, Castillo E, Vilke GM, Hopper A, Ryan V, Wilson MP. First-generation antipsychotics are still preferred in the emergency department but are often not administered with adjunctive medications. Submitted.
KETAMINE: A POTENTIAL RAPID-ACTING ANTISUICIDAL AGENT?

Samuel T. Wilkinson, M.D. and Gerard Sanacora, M.D., Ph.D.∗

Ketamine has attracted widespread attention as a potential rapid-acting antidepressant. There is also considerable interest in its use for the rapid treatment of patients deemed at risk for suicide. Here, we review the available evidence (open-label and randomized controlled trials) that examine the effects of ketamine on suicidal ideation (SI). Overall, data suggest that ketamine has a rapid albeit transient effect in reducing SI, though some studies had mixed results at different time points or using different assessments. Weaknesses to the existing literature include the small sample sizes of the studies, the exclusion of patients with significant SI at baseline from many of the studies, and the potential functional unblinding when participants are randomized to saline as placebo. The evidence supporting the clinical use of ketamine for SI is very preliminary. Although ketamine appears to a promising therapeutic option in a context where there is a great unmet need (i.e., patients at imminent risk of suicide), further controlled trials are needed to allow for meaningful clinical recommendations.

Depression and Anxiety 0:1–7, 2016. © 2016 Wiley Periodicals, Inc.

Key words: ketamine; suicidal ideation; suicide; depression; antidepressant

INTRODUCTION

Forty-two thousand seven hundred and seventy-three deaths by suicide were reported in the United States in 2014, making suicide the 10th leading cause of death of Americans of all ages.1 For individuals aged 15–44 years, suicide is among the top three causes of mortality worldwide.2,3 Beyond the devastating impact of suicide-related mortality on individuals and families, there are also tremendous economic and public health concerns associated with suicide attempts. More than 490,000 hospital visits related to suicide attempts or self-harm behavior were recorded in the United States for 2013, and the economic cost of suicide death, related mostly to loss of productivity in the United States, being estimated to be greater than $44 billion annually.4 Already aware of the tremendous societal burden related to suicidal behavior, the US Surgeon General released a Call to Action to Prevent Suicide in 1999 calling for a renewed effort to identify and develop better treatments and suicide prevention methods.5 Unfortunately, despite these efforts, suicide rates have not decreased since the 1950s,6 but have paradoxically been increasing over the past 10 years.1
Although not all suicides are associated with mental illness, it is estimated that approximately 90% of individuals who commit suicide suffer from a treatable psychiatric disorder, most commonly a mood disorder. Generally, the longer time spent in a depressive episode, the higher the chance of suicide. Evidence surrounding the efficacy of the currently available standard treatments for mood disorders in treating suicidal ideation (SI) presents a complex picture, with some evidence suggesting an overall benefit of the treatments and other studies suggesting an age-related acute worsening of SI with treatment initiation. However, in either case, it is clear that the currently available standard antidepressant treatments do not provide a robust and rapid relief of SI.

The existing treatment options for patients assessed to be at acute risk for suicide are limited. Current management of patients deemed at acute risk of suicide usually consists of hospitalization plus pharmacotherapy, psychotherapy, electroconvulsive therapy (ECT) or a combination thereof. Significant evidence supports a reduction in the long-term risk of suicide in mood disorders associated with lithium treatment, though it has not been shown to be effective in the acute setting. Clozapine has received an FDA-approved indication for “reducing the risk of recurrent suicidal behavior,” but this is primarily based on data from patients diagnosed with schizophrenia or schizoaffective disorder, and not patients with mood disorders, which constitute the largest portion of patients who commit suicide. Further, clozapine has not been shown to decrease SI in the acute setting. Even ECT, considered the most highly efficacious antidepressant treatment, may not provide a reduction in SI for 1–2 weeks. Moreover, hospitalization, which is designed to provide a safe environment for patients, is not completely effective in preventing suicide. Although uncommon, suicide among inpatients remains one of the most commonly reported sentinel events. These facts highlight the need for the development of more effective means of identifying those at risk for suicide and for the introduction of novel effective therapeutic approaches with more rapid rates of onset of antisuicidal action.

In 2000, Berman et al. first reported that ketamine, an N-methyl-D-aspartic acid antagonist, possesses rapid-acting antidepressant properties. Since then, several randomized placebo-controlled trials and case series have confirmed that the drug produces a rapid onset, transient antidepressant response in both treatment-resistant depression (TRD) unipolar and bipolar depression. Given the rapid-acting nature of ketamine and the reports of high rates of efficacy in TRD, the potential utility of the drug in the acute treatment of suicidal patients with mood and other disorders has gained great interest. Here, we review the evidence for ketamine’s effects on SI in patients with mood disorders. We first review evidence gleaned from open-label trials and case series, followed by evidence from randomized controlled trials examining ketamine’s general antidepressant properties.

We later consider whether the effects of ketamine on suicide risk are independent of the drug’s effects on mood in general and review the limited evidence specifically attempting to address the antisuicidal effect of ketamine. The promise and limitations of this approach as a treatment of suicidal thinking and behavior are considered. Except where noted, all protocols reviewed utilize an intravenous infusion of 0.5 mg/kg ketamine over 40 min.

### OPEN-LABEL AND NATURALISTIC TRIALS

Several open-label and naturalistic studies examining either single-dose or repeated-dose administrations have attempted to gain insight into the potential antisuicidal effects of ketamine (see Table 1). A study of 33 medication-free inpatients with Major Depressive Disorder (MDD, treatment-resistant) undergoing a single, open-label IV ketamine infusion, designed to assess antidepressant effects of ketamine, showed a reduction in SI in all scales employed in the study (Montgomery–Åsberg Depression Rating Scale [MADRS], Hamilton Depression Rating Scale [HDRS], Beck Depression Inventory [BDI], and Beck Scale for SI [SSI]). Pre–post effect sizes were largest at 40 min ($d = 1.05$), diminishing to moderate magnitude effect sizes at 230 min ($d = 0.45$). However, it should be noted that these effect sizes were much larger when considering only the 10 patients with high baseline SI (defined as SSI score >3) in the analysis: $d = 2.36$ at 40 min and $d = 1.27$ at 230 min. Notably, the participants in this study had stable SI as measured by the SSI for a mean period of 8 days prior to treatment. Thakurta et al. also reported on 27 inpatients with TRD (≥2 failures of antidepressants) who were given a single ketamine infusion after a 2-week washout of other antidepressant medications in India. SI was reported to be reduced in the immediate period following treatment (40–230 min) as assessed by the SSI and the HDRS, but this reduction was not sustained 24 hr following treatment. An additional open-label study of 26 medication-free patients with TRD undergoing a single intravenous ketamine infusion reported MADRS-SI scores were significantly reduced 24 hr following treatment compared to baseline levels (pre–post effect size $d = 1.37$). Implicit measures (IAT) of SI were also significantly reduced in a subset of 10 patients who completed the assessment in a pre–post comparison ($d = 1.36$). Notably, the decrease in SI was not shown to be independent of the overall reduction in depression symptoms in this study. A subset of 10 patients in the study who received six total infusions each, given three times per week, maintained a significant reduction in SI...
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Placebo</th>
<th>Intervention</th>
<th>Setting</th>
<th>Sample size</th>
<th>Diagnosis</th>
<th>SI measure</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized controlled trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Berman et al. 2000</td>
<td>Crossover, single dose</td>
<td>saline</td>
<td>0.5 mg/kg over 40 min</td>
<td>Outpatients</td>
<td>7</td>
<td>MDD, BP</td>
<td>HDRS</td>
<td>Significant decrease in HDRS-SI item compared to placebo ($P = .02$)</td>
</tr>
<tr>
<td>Price et al. 2014</td>
<td>Parallel, single dose</td>
<td>midazolam</td>
<td>0.5 mg/kg over 40 min</td>
<td>Outpatients</td>
<td>57</td>
<td>MDD, TRD</td>
<td>Implicit: MADRS, QIDS, SSI</td>
<td>At 24 hr, ketamine resulted in significantly lower explicit measures ($d = 0.82$, $P = .01$); differences between groups using IAT did not reach statistical significance. The decrease in SI was explained by overall reduction in depression symptomatology.</td>
</tr>
<tr>
<td>Hu et al. 2015</td>
<td>Parallel, single dose</td>
<td>saline</td>
<td>0.5 mg/kg over 40 min</td>
<td>Outpatient</td>
<td>30</td>
<td>MDD</td>
<td>QIDS</td>
<td>Significantly lower SI measures from 2 to 72 hr following treatment in group receiving ketamine ($d$ ranging from 1.05 to 2.24; all $P &lt; .05$).</td>
</tr>
<tr>
<td>Murrough et al. 2015</td>
<td>Parallel, single dose</td>
<td>midazolam</td>
<td>0.5 mg/kg over 40 min</td>
<td>Inpatients &amp; outpatients</td>
<td>24</td>
<td>Various</td>
<td>SSI, MADRS</td>
<td>SSI: lower in ketamine group at 48 hr ($d = 0.67$, $P = .047$) but not at 24 hr ($P = .32$); MADRS-SI: lower in ketamine at 24 hr ($d = 0.86$, $P = .05$), but not at 48 hr ($P = .077$).</td>
</tr>
<tr>
<td><strong>Open-label/case series</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Price et al. 2009</td>
<td>Open label, single dose</td>
<td>NA</td>
<td>0.5 mg/kg over 40 min</td>
<td>Inpatient for first 24 hr</td>
<td>26</td>
<td>MDD, TRD</td>
<td>MADRS (n = 26), IAT (n = 10)</td>
<td>Lower MADRS-SI scores 24 hr posttreatment ($d = 1.37$; $P &lt; .001$) in subset, IAT reduced at 24 hr ($d = 1.36$; $P &lt; .003$).</td>
</tr>
<tr>
<td>Diazgranados 2010</td>
<td>Open label, single infusion</td>
<td>NA</td>
<td>0.5 mg/kg over 40 min</td>
<td>Inpatients</td>
<td>33</td>
<td>MDD, TRD</td>
<td>MADRS, HDRS, BDI, SSI</td>
<td>Reduction in SI using all scales ($P &lt; .001$) with largest effects at 40 min, $d = 1.05$; at 230 min, $d = 0.45$. Subanalysis among those with high baseline SI yielded higher effect sizes ($d = 2.36$ at 40 min and $d = 1.27$ at 230 min).</td>
</tr>
<tr>
<td>Larkin and Beautrais 2011</td>
<td>Open label/case series</td>
<td>NA</td>
<td>0.2 mg/kg over 2 min</td>
<td>Emergency department inpatient</td>
<td>14</td>
<td>MDD</td>
<td>MADRS, SSI</td>
<td>Significant reduction in SI (MADRS) for up to 10 days following infusion ($P &lt; .001$).</td>
</tr>
<tr>
<td>Thakurta et al. 2012</td>
<td>Open label, single infusion</td>
<td>NA</td>
<td>0.5 mg/kg over 40 min</td>
<td>Inpatient</td>
<td>27</td>
<td>MDD, TRD</td>
<td>SSI, HDRS</td>
<td>Significant reduction in SSI/MADRS-SI scores from 40 min through 230 min ($P &lt; .01$). Change was not significant from day 1 onward.</td>
</tr>
<tr>
<td>Murrough et al. 2013</td>
<td>Open label, six infusions(3x/week)</td>
<td>NA</td>
<td>0.5 mg/kg over 40 min</td>
<td>Inpatient for first treatment</td>
<td>24</td>
<td>MDD, TRD</td>
<td>MADRS</td>
<td>Both responders and nonresponders showed significant reduction at 2 hr in SI ($P &lt; .05$)</td>
</tr>
<tr>
<td>Rasmussen et al. 2013</td>
<td>Open label, up to four infusions(2x/week)</td>
<td>NA</td>
<td>0.5 mg/kg over 100 min</td>
<td>Inpatients &amp; outpatients</td>
<td>10</td>
<td>MDD/BPII, SSI, SSF TRD</td>
<td>Significant reduction in SI at study end were achieved in the SSI ($P = .007$) and SSF ($P = .026$).</td>
<td></td>
</tr>
<tr>
<td>Kashani et al. 2014</td>
<td>Open label, single infusion</td>
<td>NA</td>
<td>0.2 mg/kg over 1 min</td>
<td>Emergency department</td>
<td>49</td>
<td>Not reported</td>
<td>SSI</td>
<td>Significant decrease in SSI scores over time, with 44 of 49 patients reporting no SI at 10 days</td>
</tr>
<tr>
<td><strong>Mixed</strong></td>
<td>Secondary Analysis from three RCTs, one open-label</td>
<td>saline</td>
<td>0.5 mg/kg over 40 min</td>
<td>Inpatients</td>
<td>60</td>
<td>MDD/BP, TRD</td>
<td>SSI, BDI, HDRS, MADRS</td>
<td>In patients with some baseline SI, all scales (except SSI) showed significant effect of ketamine on SI ($P &lt; .01$). Effect of ketamine on SI was independent of reduction in overall depression and anxiety measures.</td>
</tr>
</tbody>
</table>

BDI, Beck depression inventory; BP, bipolar disorder; HDRS, Hamilton depression rating scale; IAT, implicit association test; MADRS, Montgomery–Asberg depression rating scale; MDD, major depressive disorder; QIDS, quick inventory of depressive symptomatology (self-report); SSF, suicide status form; SSI, Beck scale for SI; TRD, treatment-resistant depression.
for the duration of the treatment. However, it should be noted that subjects with “highly active” SI were excluded from participation in this study. In another study of 24 TRD medication-free participants treated with six serial infusions of ketamine over 2 weeks, Murrough et al.\[10\] noted a significant decrease in SI (MADRS-SI item) at 2 hr compared to baseline in both patients ultimately considered to be treatment responders and nonresponders (defined at 24 hr by 50% decrease in symptoms). Approximately 70% of responders had relapsed by 4 weeks following the final infusion; there is no mention of the duration of ketamine’s effects on SI. Rasmussen et al.\[31\] reported on 10 TRD participants (both inpatients and outpatients) who were treated with ketamine IV 0.5 mg/kg over an extended 100 min infusion period in addition to treatment as usual (i.e., concomitant antidepressants). Participants continued to receive infusions until remission was achieved or four infusions (provided twice weekly) were given. Changes in explicit measures of SI were significant as assessed by the SSI and the SSF (Suicide Status Form) in a pre–post comparison; reduction in SI was correlated with reduction in overall depressive symptoms.

There are two open-label, naturalistic studies exploring the use of ketamine treatments in emergency department (ED) settings. Larkin and Beautrais\[32\] treated 14 patients with significant SI recruited from the ED with 0.2 mg/kg ketamine delivered IV over 1–2 min along with treatment as usual. They reported that SI decreased significantly in all patients at the 40-, 80-, 120-, and 240-min time points after ketamine administration using the MADRS-SI, and no evidence of recurrence was detected during the 10-day follow-up period. Another trial of 49 medication-free patients presenting to the ED of Imam Hossein hospital in Tehran for SI received a single dose of 0.2 mg/kg ketamine, delivered IV over 1 min along with treatment as usual.\[33\] The investigators reported a significant decrease in SSI scores over the 2-hr period following ketamine dosing, and 94% of the patients reported no SI at day 10. Although these two studies provide some evidence to suggest the feasibility and potential benefits of using ketamine in the ED setting to treat SI, the value of these studies is markedly limited by shortcomings in the study designs, including small sample sizes, lack of diagnostic specificity, no comparison groups or historical subject comparisons, and the unique choice of dosing compared to other existing studies.

**RANDOMIZED CONTROLLED TRIALS**

In their original study of ketamine in medication-free outpatients with MDD, Berman et al.\[21\] specifically noted significant decreases in SI HDRS-SI item (not adjusted for multiple comparisons) shortly following a single ketamine infusion in their original report on the drug’s antidepressant efficacy (see Table 1). Since that report, there have been several other accounts of secondary analyses attempting to gain insight into the relationship between ketamine and SI using data from randomized controlled ketamine studies that were not originally designed to examine effects on SI. Ballard et al.\[34\] examined the data from three placebo (saline)-controlled RCT’s including participants with both MDD and bipolar disorder, and one open-label study conducted at the NIMH. In the total sample of 133 subjects, after controlling for both depression and anxiety symptom clusters in a regression model, ketamine exerted an effect on SI that was independent of its effects on depression and anxiety. Restricting the analysis to 57 subjects who participated in a randomized study and demonstrating the presence of some SI at baseline (HDRS SI item score >0), there was again evidence of an independent effect of ketamine on SI. Thus, this evidence suggests that ketamine exerted an independent effect on SI as opposed to this effect being mediated solely by an overall reduction in depressive or anxiety symptoms. Overall, this secondary analysis suggests that ketamine’s effects on SI may in fact be independent of its effects on other depression or anxiety symptoms. Moreover, further analysis from the same datasets using a slightly broader definition of SI found ketamine to have significant effects on SI rating on all scales, with the exception of the total score of the SSI, but there were significant effects noted as measured by the abbreviated SSI5 scale.\[35\] Consistent with the previous reports showing large effects of a single ketamine infusion on SI, a recent study randomizing 30 patients with MDD to ketamine infusion plus escitalopram or saline infusion plus escitalopram at Beijing Chao-Yang Hospital,\[36\] found the subjects in the ketamine/escitalopram group had lower explicit measures of SI (as measured by Quick Inventory of Depressive Symptomatology [QIDS] SI item) compared to the placebo/escitalopram group from 1 to 72 hr following treatment, with Cohen’s $d$ ranging from 1.05 to 2.24 during this time period. These participants were outpatients and, other than the concomitant initiation of escitalopram on the first treatment day, were free of other psychotropic medication.

Analyzing data from 57 outpatients with TRD assessed using explicit measures (a composite measure of SI scores from various scales) and implicit measures (derived from an IAT) of SI at baseline and 24 hr following a single infusion of ketamine or midazolam, Price et al.\[37\] reported SI scores 24 hr postinfusion were reduced in those receiving ketamine compared to midazolam in explicit measures, but difference between groups at 24 hr using two variants of IAT measures, identified in the previous open-label study, did not reach statistical significance in omnibus analyses. Notably, subjects with “serious and imminent” SI were excluded from participation. Also, in this study the decrease in explicit measures of SI appeared to be explained by the overall decrease in depressive symptoms.

Murrough et al.\[38\] recently completed the only randomized trial thus far designed specifically to assess the effect of ketamine on SI. A sample of 24 subjects with significant SI (13 with MDD, 7 with bipolar disorder, 3 with PTSD) recruited from both inpatient and
outpatient settings were randomized to a single-dose infusion of intravenous ketamine or 0.045 mg/kg intravenous midazolam (active control) over 40 min, added on to their existing medication regimen. Although this likely underpowered study failed to show a significant effect of ketamine treatment on the primary outcome measure (group difference in SSI at 24 hr), the ketamine treatment group had lower SSI scores at 48 hr and the MADRS-SI item (secondary outcome) was significantly lower in the ketamine group at 24 hr but not at 48 hr.

Overall, data from RCTs suggest that ketamine has a rapid effect in reducing SI, though some studies had mixed results at different time points or using different assessments. However, it should be noted that there are several major weaknesses regarding the quality of data available evaluating the antisuicidal effect of ketamine generated from these studies. One weakness of this literature is that, with the exception of Murrough et al.,[38] these RCTs were designed primarily to test ketamine’s antidepressant effects and, in many cases, patients with clinically meaningful SI, or thought to be at imminent risk of suicide, were excluded from participation. Further, it should be emphasized that most studies measured SI only as a secondary outcome, and some measured SI by a single scale item that is part of a general depression scale, rather than a scale designed to measure SI (SSI). Among patients receiving ketamine, the individual SI items of the MADRS, HDRS, and BDI have been shown to correlate with the abbreviated five-item SSI, but not with the full scale.[35]

Another weakness of these studies is that most are generally of small sample size, limiting their power to detect group differences. Nonetheless, despite this limitation, there is converging evidence that ketamine may rapidly reduce SI. A third significant limitation is the potential functional unblinding that may occur due to the dissociative properties of ketamine. It is quite probable that most subjects become functionally unblinded; evidence for this is seen in the extremely low placebo response rates seen where saline infusion is used as the control. More recently, some trials have used midazolam as an active comparator to reduce the amount of functional unblinding. Although it is unclear whether using midazolam as the active comparator completely resolves the problem of unblinding, these trials generally have higher placebo response rates and, hence, lower between-group effect sizes, but still appear to show meaningful differences with ketamine treatment.

**DISCUSSION**

The collective existing data provide intriguing preliminary evidence suggesting that ketamine may produce uniquely rapid effects on SI. However, both the open-label and placebo-controlled trials have many limitations that restrain our ability to draw firm conclusions at this point in time. Fortunately, the results of several clinical trials evaluating the efficacy of ketamine or esketamine (S-enantiomer) to stabilize patients in need of hospitalization due to risk of suicide (clinical trials identifier: NCT02133001, NCT02299440) or outpatients with significant SI (NCT02094898; NCT01700829) should provide more reliable data related to ketamine’s antisuicidal effects in the relatively near future.

Although, as discussed in the introduction, there is a great unmet need for more robust and rapidly acting antisuicidal treatments, the evidence to date supporting the clinical use of ketamine for this purpose is extremely preliminary. Any consideration of the clinical use of ketamine should weigh heavily the known risks of the treatment approach (can we reference another paper in this issue?), the limited evidence of efficacy, and any possible delays it may cause in receiving established treatments for reducing the risks of SI and behavior, such as ECT, lithium, or clozapine. Moreover, there remains little data of strategies for maintaining the antisuicidal properties of ketamine, and concerns exist regarding the repeated administration of ketamine.[39] Finally, all studies reviewed examined the effects of ketamine on suicidal ideation, not on suicidal behavior; whether ketamine’s effects on SI translate into effects on suicidal behavior has not been studied.

There is also significant interest in the question of whether ketamine’s effect on SI is independent of its general antidepressant effects (i.e., pseudospecificity). The issue of pseudospecificity could impact the path to FDA approval of ketamine or related medications for use in the treatment of SI or behavior. The FDA has considered claims for drug effects in psychiatric illnesses to be pseudospecific if it is found to be artificially narrow (i.e., focusing on a particular aspect or symptom of an illness) in the absence of any empirical evidence to support such a restricted focus.[40] For example, to evaluate the claims of pseudospecificity with regard to negative symptoms in schizophrenia, the FDA asked the following questions: (1) Are negative symptoms phenomenologically distinct from other symptoms of schizophrenia?; and (2) do they have a course that is distinct from other symptoms?[41] It could be assumed that the agency will take a similar view on claims of antisuicidal effects of ketamine or related compounds in mood disorders. To date, the literature on whether ketamine has a specific effect on SI or whether reductions in SI are mediated by an overall reduction in general depression symptoms is inconclusive. Although some data suggest the antisuicidal effect to be present across different diagnostic groups, it is limited by the relatively small sample sizes and the fact that the participants enrolled in the studies had minimal or no baseline SI. Larger controlled studies are clearly needed to more definitively address this question.

In sum, ketamine (at least at 0.5 mg/kg i.v. infused over 40 min) appears to represent a promising treatment for patients with SI. However, more data are clearly needed, especially in patients with elevated baseline levels of SI, prior to making any meaningful clinical recommendations on the utility of the treatment. Although there are some interesting data suggesting the effects of ketamine may reduce SI independently of its more general effects...
on mood and anxiety, this will need to be examined in greater detail in future studies in order to address the issue of pseudospecificity. Future studies will also need to determine if ketamine-induced effects on SI and behavior will be generalizable to patients who do not suffer primarily from a mood disorder (i.e., PTSD, obsessive-compulsive disorder, alcohol abuse). Other drugs with putative rapid-acting antidepressant effects also in development will be subjected to similar concerns, and will require studies designed to specifically address the unique aspects of SI and behavior to establish efficacy and possible FDA approvals. As with all treatments, the risks of ketamine must be weighed against potential benefits in considering future development of the treatment strategy in the clinical setting.

Acknowledgments. This work was supported by a grant from the National Institute of Mental Health, 5R25MH071584-09 (STW), and by the Connecticut Department of Mental Health and Addiction Services (GS).

REFERENCES


A Word to the Wise About Ketamine

Recent reports of an acute antidepressant effect for intravenous ketamine, a schedule III agent used in anesthesia and pain clinics, have generated considerable hope and enthusiasm among both researchers and clinicians (1–4). The response partly reflects hope that a new mechanism of antidepressant action has been discovered and highlights the scarcity of agents that clinicians can administer to produce immediate effects on mood. Positive initial research reports (including the recent article in the Journal by Murrough et al. [4]) have unintentionally engendered growing off-label clinical use of ketamine in emergency rooms, specialty pain clinics and, most recently, free-standing private psychiatry clinics. If ketamine were a new drug, then the Food and Drug Administration would have required hundreds more patients to be rigorously studied before an approval for general distribution. However, because ketamine was already approved as an anesthetic, any physician can legally prescribe it. Some practitioners have even commissioned pharmacists to compound intranasal and other formulations. This unbridled enthusiasm needs to be tempered by a more rational and guarded perspective.

We Need To Know More About Acute and Longer-Term Efficacy and Risks

The data on clinical response to ketamine as an antidepressant are still relatively limited. The study by Murrough et al. (4) was the largest to date but still included only 47 patients treated with the drug. Will the data hold up in other controlled trials? The antidepressant effects of ketamine are generally short lived, lasting less than 1 week, although longer than its half-life. Unfortunately, to date we have no idea what we should do for follow-up therapy. In a recent report (3), repeated ketamine administration every few days appeared to be effective over a 2-week period with no clear tachyphylaxis to either the antidepressant or depersonalization effect, but that does not address what to do beyond 2 weeks, including dealing with the risk for dependence since ketamine is a drug of abuse.

Ketamine produces feelings of depersonalization and even psychosis (1–4), and it was previously used to test hypotheses regarding dopamine and glutamate in schizophrenia. In their study, Murrough et al. (4) undertook stringent patient evaluations to decrease the risk of psychotic reactions, but such evaluations may not be occurring in other settings. Clinicians outside a research setting generally do not have the resources to screen patients similarly.

We Need To Know More About the Mechanism of Action of the Mood-Elevating Effects

The antidepressant effect has been thought to reflect ketamine’s glutamatergic properties, specifically its blocking of N-methyl-D-aspartic acid (NMDA) receptors, which should be a clue for follow-up therapy. However, other currently available agents (covering a variety of glutamatergic actions) have proven unsuccessful in antidepressant trials either as monotherapy or in combination with ketamine (5–7). Investigational agents have been mixed in their effects, with glycine partial or full agonists that act essentially as NMDA agonists also being effective for depression (unpublished 2012 report by R.M. Burch; 8, 9). This suggests
that NMDA antagonism may not be the primary mechanism of action for ketamine in major depression. Recent reports have indicated that ketamine has effects on intracellular mTor that could account for its antidepressant properties (10).

Stimulants and opiates have long been associated with short-term, although generally clinically ineffective, therapeutic effects and problems with abuse. Ketamine has both opiate and stimulant effects (11, 12). It is a strong promoter of catecholamine, particularly dopamine, turnover (12), and its monoaminergic properties are similar to cocaine or amphetamine. Ketamine also has mu opioid receptor properties, consistent with its use for anesthesia and treatment of pain. This mechanism may be similar to the antidepressant effects of buprenorphine (13), although a study in healthy individuals did indicate that the effects of ketamine on responses to alcohol were not blocked by the mu antagonist naltrexone (14). To our knowledge, such a study has not been conducted in depressed patients. It is interesting that Rodriguez et al. (15) recently reported that ketamine given intravenously was similarly effective in refractory obsessive-compulsive disorder (OCD). This was reminiscent of a double-blind, placebo-controlled study by Koran et al. (16) a few years ago that reported that oral morphine improved OCD symptoms 1 day after administration—an effect that lasted 5 days. Comparison studies against stimulants and opioids would be helpful for assessing ketamine’s mechanism of action for acutely elevating mood and its potential for providing overall benefit in the treatment of depression.

**Should Clinicians Prescribe Ketamine for Patients With Refractory Depression?**

Without more data on what ketamine can do clinically, except to produce brief euphoriant effects after acute administration, and knowing it can be a drug of abuse, it is difficult to argue that patients should receive an acute trial of ketamine for refractory depression. Some ketamine investigators have argued for not using it outside of a hospital setting (17), but without extensive experience and a follow-up strategy, is even that the most prudent strategy? I would argue that waiting until we understand more about its effects and risks makes most sense. Patients have not benefitted in the past from the overuse of short-term treatments such as stimulants and opiates. The results have been toxicity and dependence from the immediate treatment and a failure to recommend and follow through with more definitive longer-term treatments required for patients with depression. The recent ketamine studies are exciting, and they open up important avenues for investigation that should be supported; however, until we know more, clinicians should be wary about embarking on a slippery ketamine slope.

**References**


Until we know more, clinicians should be wary about embarking on a slippery ketamine slope.


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Dr. Schatzberg has received consulting fees from Bay City Capital, BrainCells, CeNeRx, Cervel, Eli Lilly, Genentech, Gilead, Jazz, Lundbeck/Takeda, McKinsey, Merck, MSI, Naurex, Neuronetics, Novadel, PharmaNeuroBoost, Sunovion, Synosia, and Xhale. He has equity in Amnestic, BrainCells, CeNeRx, Cervel, Corcept (co-founder), Delpor, Forest Labs, Merck, Neurocrine, Novadel, Pfizer, PharmaNeuroBoost, Somaxon, Synosia, Titan, and Xhale. He is a named inventor on pharmacogenetic use patents on prediction of antidepressant response and glucocorticoid antagonists in psychiatry, and he has received speakers’ honoraria from Merck. Dr. Freedman has reviewed this commentary and found no evidence of influence from these relationships.