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

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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 Duplicate articles, unpublished reports, abstracts, and review articles were also excluded.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.

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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 involved in the final review.

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.

Table 1
Characteristics of the Studies Included in the Review

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Comparison [Number of Patients Assigned]</th>
<th>Outcome</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Messenger et al., 200816</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>
</tr>
<tr>
<td>Galinski et al., 200717</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>
</tr>
<tr>
<td>Kennedy et al., 199818</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., 200719</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>
</tr>
</tbody>
</table>

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.\(^\text{18}\) 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.\textsuperscript{18} Cases of neuropsychological adverse events were reported.\textsuperscript{17,18} 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.\textsuperscript{16–19}

Two studies reported a reduction in the amount of adjuvant opioids consumed by patients who received ketamine. Galinski et al.\textsuperscript{17} 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). Gurnani et al.\textsuperscript{19} 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.\textsuperscript{16–19} There was evidence of unclear documentation or missing records. Data on the use of adjuvant analgesic therapies were lacking. \textsuperscript{16} Detailed descriptions of reported adverse events were not available.\textsuperscript{17} 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\textsuperscript{18,19} or adverse events\textsuperscript{16–19} were not consistently presented.

In the trial by Messenger et al.\textsuperscript{16} 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.\textsuperscript{17} used the lowest dose of ketamine. It is unclear whether this had an effect on the study results.

Kennedy et al.\textsuperscript{16} and Gurnani et al.\textsuperscript{19} detected detectable 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.\textsuperscript{21–23} All three studies reported satisfactory pain reduction for most patients within 30 minutes of therapy. Cases of neuropsychological adverse events were reported.\textsuperscript{17,18} 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.,\textsuperscript{24} 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.,\textsuperscript{25} 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 dysthria was reported in one of 35 (2.8%) patients. Incomplete data were noted in 22.8% of cases.

Richards and Rockford\textsuperscript{26} 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.\textsuperscript{27} 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.\textsuperscript{28} 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,\textsuperscript{16,17,19} and incomplete descriptions of adverse events\textsuperscript{17} or pain scores,\textsuperscript{19} 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.