TAKE-HOME MESSAGE

According to limited evidence, low-dose ketamine and morphine appear to provide similar levels of pain relief at 30 minutes; however, low-dose ketamine is associated with a higher rate of self-limited neuropsychological adverse events.

Is Low-Dose Ketamine an Effective Alternative to Opioids for the Treatment of Acute Pain in the Emergency Department?

EBEM Commentators
Michael Gottlieb, MD
Kelly W. Ryan, MD
Christine Binkley, MD, MPH
Department of Emergency Medicine
Rush University Medical Center
Chicago, IL

METHODS

DATA SOURCES

MEDLINE, EMBASE, Allied and Complementary Medicine Database, the Cumulative Index of Nursing and Allied Health, PubMed, the Cochrane Controlled Trial Registry, the Cochrane Database of Systematic Reviews, and ClinicalTrials.gov were searched from inception through February 2015 for relevant studies. Manual searches of abstracts presented at selected emergency medicine and anesthesia conferences from 2012 to 2014 were also performed. The investigators reviewed the bibliographies of included articles and contacted the authors for additional relevant references. The search strategy was limited to randomized controlled trials and observational studies of human subjects published in English.

STUDY SELECTION

The authors asked the following question, using the formatting population, intervention, control, outcome (PICO): "In adult patients requiring acute pain management in the emergency department (ED) (*P*), does the use of low-dose ketamine as an adjunct or alone (*I*), compared with using opioids (*C*), offer improved pain control, decrease the need for opioid analgesics, or decrease the occurrence of adverse events (*O*)?" Eligible studies compared participants receiving low-dose

Results

The search identified 1,396 articles, of which 44 were deemed eligible for full-text review. Of these, a total of 8 articles (n=609 patients) were included in the final qualitative analysis. The review included 6 randomized controlled trials and 2 observational studies. Five studies were conducted in the United States, with the remainder conducted in France, India, and Iran. Most of the randomized controlled trials used low-dose ketamine, with doses ranging from 0.1 to 0.5 mg/kg given intravenously; however, one study followed the initial intravenous dose with a subcutaneous infusion at 0.1 mg/kg per hour.[3] Another study that used a dose of 0.5 mg/kg gave patients concomitant midazolam at 0.3 mg/kg in the treatment group only.[4] The comparator group included intravenous morphine at 0.05 to 0.1 mg/kg in all 6 of the included randomized controlled trials. In terms of analgesic effect, the 6 randomized controlled trials were rated as moderate quality, whereas the 2 observational studies were rated as very low quality.

Overall, moderate-quality studies did not demonstrate a significant difference in pain scores between the low-dose ketamine and opioids. There was insufficient evidence to determine whether low-dose ketamine reduced the need for rescue analgesia because of limitations of the data from the 3 studies assessing this outcome. There was an increased risk of adverse effects in the low-dose ketamine group compared with the morphine group (15.4% versus 4.4%). Adverse effects included agitation, hallucinations, dysphoria, and confusion; however, they were self-limited and there were no significant differences in rates of respiratory depression.

Commentary

Ketamine is a well-known agent used for procedural sedation in the ED, most commonly used in pediatric patients.[5] Compared with other agents, ketamine offers the

ketamine regardless of route or dose regimen with any opioid analgesic among adult patients (>18 years) requiring acute pain management for any condition in the ED. Initial study selection was assessed by 2 independent reviewers, with articles being included for full-text review according to title and abstract or if there was disagreement or uncertainty about article content. Final article inclusion was determined by one reviewer using standardized and piloted selection criteria. Equivocal decisions for final inclusion were resolved by consensus among all of the investigators.

DATA EXTRACTION AND SYNTHESIS

Two investigators extracted data with a predesigned form that included variables such as year, country, study design, clinical setting, low-dose ketamine and comparator dose or route or need for redosing, pain scores, and adverse outcomes. Study strength was determined with the Grading of Recommendations Assessment, Development, and Evaluation criteria.[1] Risk of bias was assessed with the Cochrane Collaboration Risk of Bias tool.[2] Meta-analysis was planned but not performed because of significant heterogeneity with respect to outcomes, methods, and indications for low-dose ketamine among the included studies.

advantage of providing analgesia while protecting the respiratory drive.[5] More recently, investigators have explored the use of subdissociative doses of ketamine (ie, low-dose ketamine) for acute pain management.[6] Low-dose ketamine is typically considered to be doses of less than 1 mg/kg, although most studies use 0.1 to 0.3 mg/kg.[7] Although there have been a number of studies performed in the postoperative setting that demonstrate evidence of a morphine-sparing effect,[6] the evidence in the ED setting is limited.

This systematic review provides a qualitative analysis of 8 studies assessing the use of ketamine to treat acute pain in the ED setting. Although the results suggest that ketamine has efficacy similar to that of morphine, with a low rate of self-limited neuropsychiatric adverse effects, it is important to consider several limitations. First, the number of studies (N=4) and patients (n=225) assessing the ability of ketamine to reduce opioid use was small. Moreover, there were variations in the patient populations with respect to baseline characteristics and type of pain. There were also differences in the routes and doses of ketamine, as well as the use of adjuvant benzodiazepines and opioids. Furthermore, the outcome criteria varied significantly between trials, with differences in primary outcomes and methods of pain scale assessment (eg, numeric rating scale, visual analog scale, summed pain intensity difference). Finally, the definitions of adverse events were different between trials, with some providing empiric benzodiazepines to reduce the risk of emergence reactions.

Although this review provides preliminary evidence that low-dose ketamine may be used as an alternative to opioids for acute pain in the ED setting, studies with larger sample sizes and more rigorous methodology are needed to establish patient selection criteria and the best dosing strategy.

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Ghate G, Clark E, Vaillancourt C. Systematic review of the use of low-dose ketamine for analgesia in the emergency department. *CJEM*. 2017; https://doi.org/10.1017/cem.2017.48.**

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Michael Brown, MD, MSc, Jestin N. Carlson, MD, MS, and Alan Jones, MD, serve as editors of the SRS series.