

Is Low-Dose Ketamine an Effective Alternative to Opioids for Acute Pain?



TAKE-HOME MESSAGE

In adult emergency department (ED) patients with acute pain, low-dose intravenous ketamine (0.3 to 0.5 mg/kg) may provide pain relief within 10 minutes that is similar to that of single-dose intravenous morphine (0.1 mg/kg).

METHODS

DATA SOURCES

A medical librarian searched MEDLINE, EMBASE, Scopus, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects from inception through February 2017. The Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform were searched for gray literature, and bibliographies were searched for additional citations. Only English-language studies were included.

STUDY SELECTION

Two reviewers screened all titles and abstracts, and discrepancies were resolved by discussion or an adjudicator. Included studies were randomized trials of low-dose intravenous ketamine less than or equal to 0.5 mg/kg compared with intravenous opioids in adult ED patients with acute pain (≤ 1 week's duration). Studies had to report a change in either a visual analog scale or numeric rating scale score within 60 minutes.

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Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshots (SRS) series. The source for this systematic review snapshot is:

Karlow N, Schlaepfer CH, Stoll CRT, et al. A systematic review and meta-analysis of ketamine as an alternative to opioids for acute pain in the emergency department. *Acad Emerg Med.* 2018;25:1086-1097.

Results

Ketamine versus morphine for acute pain in the ED (outcome at 10 minutes).

Study	Sample Size	Indication	Ketamine Dose (mg/kg)	Difference in Δ NRS* Score (95% CI)
Majidinejad ¹	126	Long bone fracture	0.5	-0.45 (-1.26 to 0.36)
Miller ²	45	Abdomen, flank, or musculoskeletal pain	0.3	0.82 (-0.64 to 2.28)
Motov ³	90	Abdomen, flank, or musculoskeletal pain	0.3	1.20 (-0.05 to 2.45)
Meta-analysis	261			0.42 (-0.70 to 1.54)

NRS, Numeric rating scale; CI, confidence interval.

*The NRS is a 10-point scale in which 10 is the most severe pain. Positive values indicate ketamine resulted in greater Δ NRS score.

The search identified 237 unique citations, and 3 trials (N=261) met the inclusion criteria of the review. All studies reported mean numeric rating scale score and used a single dose of morphine at 0.1 mg/kg as the control. One study evaluated ketamine at 0.5 mg/kg in patients with long bone fractures. The other 2 trials used ketamine at 0.3 mg/kg and

included patients with abdominal, flank, or musculoskeletal pain. Two trials reported mean pain scores at multiple points, up to 120 minutes, but only the results for the primary outcome of pain reduction at 10 minutes were pooled. Risk of bias was generally low for the 3 studies, but there was substantial inconsistency in which adverse events were

DATA EXTRACTION AND SYNTHESIS

Mean visual analog scale or numeric rating scale score, mean changes, and SDs were abstracted for all points less than or equal to 120 minutes, although details of data abstraction were not reported. The primary outcome was change in mean pain score at 10 minutes or closest point to 10 minutes with available data. The secondary outcome of adverse events was not predefined, but all adverse events reported in the individual trials were recorded. The difference in change in visual analog scale or numeric rating scale score between ketamine and opioids was meta-analyzed with random-effects models. Results were reported with 95% confidence intervals. The quality of individual trials was assessed with the Cochrane Risk of Bias Tool.

reported and at what points they were assessed.

The pooled analysis had high heterogeneity and did not identify a difference in numeric rating scale score change (Table). Adverse events, primarily consisting of dizziness, disorientation, and nausea, were not meta-analyzed, and all events were determined to be minor.

Commentary

Low-dose ketamine for acute analgesia in the ED is gaining popularity, with a number of recent trials suggesting efficacy similar to that of traditional opioid analgesics.¹⁻³ Alternatives to opioid analgesia have been sought because of the risk of adverse events such as hypoxia and

potential for opioid misuse. This systematic review and meta-analysis found that in ED patients with acute pain, low-dose intravenous ketamine provided pain relief at 10 minutes comparable to that of intravenous morphine at 0.1 mg/kg. This is consistent with results of previous reviews using broader inclusion criteria.^{4,5}

There are important limitations to the identified evidence, which downgraded confidence in the conclusions. The number of included studies and patients was small. Adverse events were more common with ketamine in all 3 trials but were not reported in a standard fashion and could not be pooled. Comparison of ketamine with a single dose of opioid was selected to limit confounding from cointerventions. However, evidence suggests intravenous morphine at 0.1 mg/kg may be inadequate analgesia for most patients with severe pain.⁶ Optimal opioid dosing varies widely between patients⁷ and often requires titration.⁶ Additionally, the timing of the primary outcome—change in pain score at 10 minutes—was arbitrary and likely favored ketamine. No results beyond 15 minutes were pooled and no firm conclusions past that point should be drawn. Ketamine-treated patients required more rescue medications. Finally, various causes of pain in the studies, as well as ketamine dosing, could have contributed to clinical heterogeneity.

Since the search was completed, at least 3 additional studies (516 total patients) meeting the inclusion criteria of the review have been published. Consistent with the findings from this review,

none found a difference in efficacy at less than 15 minutes between ketamine and morphine at 0.1 mg/kg. Results in regard to frequency of adverse events and efficacy at later points were mixed.⁸⁻¹⁰

This study suggests that low-dose intravenous ketamine provides analgesia comparable to that of intravenous morphine at 0.1 mg/kg.¹¹ However, it is unclear how ketamine compares with titrated opioids or whether it can be effectively redosed or titrated. Further inquiry is needed to answer these questions, as well as to explore the utility of ketamine as an adjunct to opioids.

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