UAMS Journal Club
February 2023
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Safety and efficacy of low dose ketamine compared to opioid pain medications for management of acute pain presentations to emergency department

Clinical Bottom Line

Acute pain is a common presentation in the ED and alternatives to opioids are needed for management. When comparing ketamine to opioid medication for the management of acute pain, we had concerns about the varied and high dosing in the included studies, as well as heterogeneity. Therefore, we can't confidently conclude that ketamine is as effective, or more effective, than morphine to support this medication as a replacement for opioid treatment of acute pain. The decision to use of ketamine should remain on a case-by-case basis. More studies are needed to support a change in clinical management for acute pain from opioids to ketamine.

PICO Question

In patients with acute pain, are there advantages in terms of pain control and/or side effects when using ketamine as an alternative to traditional pain control (e.g. opioids)?

P- Patents over 18 years of age presenting to emergency department with acute pain
I- Low dose ketamine (0.2-0.5 mg/kg IV)
C- IV opioids
O- Pain control at measured time intervals, need for rescue pain medication, adverse effects including nausea and hypoxia.

Background

A substantial percentage of presentations to the emergency department are due to acute pain. Though there are many options for pain control, the mainstay of therapy for acute pain are opioid medications. In recent years, physicians, pharmaceutical companies and pharmacies have been scrutinized for their role in the opioid epidemic and an effort has been made from within the medical sphere to pursue non-opioid medications for pain control. One medication which has showed promise is low-dose ketamine. Ketamine is an NMDA antagonist medication which has a variety of uses ranging from treatment of depression to procedural sedation. At low doses, ketamine has been shown to be a potent pain control medication. However, ketamine has been stigmatized due to certain adverse effects (including the feared complication of laryngospasm) as well as its emergency as a drug of abuse. The systematic reviews discussed compare low-dose ketamine to morphine or other opioids in terms of pain control as well as adverse effects.

Trial 1

Balzer N, McLeod SL, Walsh C, Grewal K. Low-dose Ketamine For Acute Pain Control in the Emergency Department: A Systematic Review and Meta-analysis. Acad Emerg Med. 2021 Apr;28(4):444-454. doi: 10.1111/acem.14159. Epub 2021 Jan 2. PMID: 33098707.

Pubmed link: https://pubmed.ncbi.nlm.nih.gov/33098707/

The Basics:

This study was a systematic review and meta-analysis of patient information obtained through Medline and EMBASE EMR records were searched for randomized control trials (RCT) comparing LDK to morphine for acute pain control in the emergency department. Eight RCTs for a total number of 1,191 patients.

Inclusion Criteria:

Studies published in English language that compared IV LDK to IV morphine in prehospital or emergency department for acute pain from any source.

Exclusion Criteria:

Excluded pediatric patients (any patient less than 18 years of age), use of ketamine outside of prehospital or ED setting, and combination therapy with LDK.

Primary Outcome:

Difference in reported pain using 10-point numeric pain reporting scale between LDK and morphine (0.1 mg/kg) at 0-15 minutes, 16-30 minutes, 31-45 minutes, 46-60 minutes and 60-120 minutes

Secondary Outcomes:

Need for rescue medication (ie insufficient pain control with initial dose of medication resulting in redosing of medication or dosing of different medication), and proportion of adverse effects (this study focused on nausea and hypoxia)

Results

Researchers reported that LDK is an effective alternative to opioids for acute pain based on their finding that there was no statistically significant difference in pain scores between LDK and morphine within the first 60 minutes. They also reported that after 60 minutes there was a slight difference of pain scores favoring morphine as more effective, but that this difference was “quite small and may not represent a clinically important significant difference”. The paper states that

there was no significant difference in the proportion of participants that required rescue medications between the two groups.

Regarding the measured adverse effect of hypoxia, the paper reports that there was no significant difference between the two groups, but mentions that there were a smaller absolute number of hypoxic events in the LDK group (3.9% vs 14.4%). Nausea was reported in both groups at nearly identical numbers, no significant difference reported between the two groups.

Limitations/Bias:

Unfortunately, the paper discussed had rather severe limitations that make its conclusions difficult to accept. The studies compared varied according to the dosage of LDK that was given, ranging from 0.2 mg/kg to 0.5 mg/kg. It is important to note that the accepted dosage for pain-dose ketamine is widely considered to be 0.1 to 0.3 mg/kg. The dose of morphine given was 0.1 mg/kg in all studies, which represents another limitation of this study. While 0.1 mg/kg of morphine is the recommended dosage for acute pain, it is generally dosed in smaller amounts (eg 4 or 5 mg) due to the size of the container that it comes in and providers being hesitant to give larger amounts. Though this would likely support ketamine's efficacy in terms of pain control vs the standard dose of morphine, this was not measured in this study and cannot be reasonable extrapolated.

Another limitation of the study was that the type of pain was not controlled for. The studies included measured pain from sickle cell pain crises, renal colic, long bone injuries, abdominal pain and back pain. It is reasonable to suspect that the etiology of the pain had some effect on the reported pain scores as well as the need for rescue medication across these studies.

The final major limitation was the inclusion of multiple small studies that sued different methods. It appears that this was necessary to include enough patients to adequately power the meta-analysis, however there are significant variations between studies that suggest variable methods between studies that influenced outcomes. By comparing the Forrest plots and noting the considerable overlap between them, we are able to deduce that there was significant heterogeneity, likely as a result of varying methodology.

With regard to bias, the researchers who conducted the data review could not be blinded, which introduced a source of bias.

Trial 2:

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(10):1086-1097. doi:10.1111/acem.13502

Pubmed link: https://pubmed.ncbi.nlm.nih.gov/30019434/

Clinical Summary: The paper is a systematic review comparing “low-dose ketamine” at doses of less than or equal to 0.5 mg/kg as a single bolus against IV opioids in effectiveness at reducing pain scale rating in a period of 60 minutes or less, in adults ages 18-65 years with acute pain lasting less than 1 week. While the review suggests that in comparing the two management options, that ketamine appears to be non-inferior to opioid for treatment of acute pain, the statistical analyses demonstrate large heterogeneity between the trials which indicate that this study should not or cannot be used to draw inferences or make definitive changes in management.

Background: Acute pain is one of the most common presenting complaints in the emergency department and treatment options for acute analgesia have seemingly been limited to opioid for management of moderate to severe pain. Opioid misuse and overuse has led to the exploration of alternative treatment options by many groups such as opioid free EDs and the Alternatives to Opioid programs with the goal to research safe, comparable and effective alternatives. One of the alternatives suggested is low dose ketamine which has been used in the ED setting for agitation and sedation however research supporting ketamine as an acute pain treatment is still needed to alter current management.

Inclusion Criteria:

The inclusion criteria for the meta-analysis included randomized clinical trials which included the following:

- Randomized control trials
- Compared analgesic effect of low dose ketamine </= 0.5 mg/kg administered as a bolus, slow push, or short infusion vs. IV opioids for acute pain
- Primary outcome change in either visual analog scale or numeric rating pain scale from baseline to second pain score within 60 minutes of intervention
- ED setting
- Adult patients aged greater than or equal to 18 years of age
- Acute pain was defined as pain beginning within the previous week

Exclusion Criteria:

- Studies which did not report visual analog or numeric rating scale pain score
- Co-administration of a pharmacologically active substance less than 20 minutes after IV ketamine or IV opioid administration
- Included a placebo comparison group

Primary Outcomes:

1) Difference in pain score after the administration of ketamine or an opioid from baseline 10 minutes after administration
2) Mean and standard deviation/standard error of change in VAS/NRS score from baseline to a specific second time point postintervention (10 minutes)

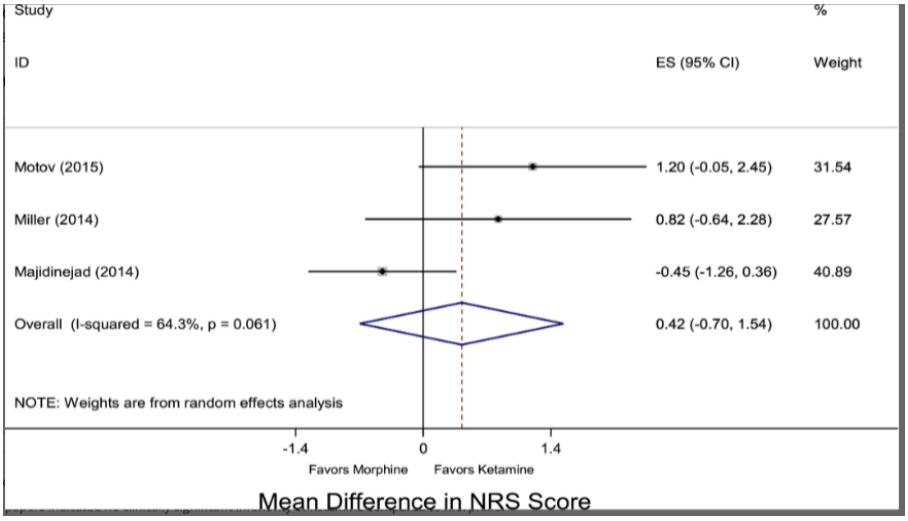
3) 10 minute time point chosen as it was commonly reported for acute pain relief in opioid and ketamine trials

Secondary Outcomes:

Secondary outcomes were not defined, though information regarding all adverse events were reported as well as measures of inadequate analgesia per authors.

Results:

Three trials met the inclusion criteria for inclusion in the meta analysis, which included a total of 261 patients. Dosing among trials was reportedly similar as well as morphine, though the dosing was not specified in this study. Two of three trials occurred in the U.S. while the other occurred in Iran. Primary outcome data analysis involved calculating the standard error of change in the VAS and NRS, though only two studies were used to compare which shared deidentified information to allow analysis. Studies per report demonstrated no clinically statistical difference between reduction in pain scores when patients were given ketamine or opioids. The pooled estimate of mean change in pain scores between ketamine and morphine suggested that ketamine was “statistically noninferior” to morphine as an analgesic with a mean change of 0.42 in pain scores between morphine and ketamine (CI= -.70 to 1.54).



Secondary outcomes were not able to be analyzed via meta analysis due to degrees in difference of the adverse events and overall adverse event rates were not calculated. However, adverse events were identified at 15, 30, 60, 90 and 120 minutes and overall event rates were reported.

	Ketamine			Morphine		
	Miller Within 120 Minutes	Motov *t* = 0 Minutes	Motov *t* = 15 Minutes	Miller Within 120 Minutes	Motov *t* = 0 Minutes	Motov *t* = 15 Minutes
Any	12 (50)	33 (73)	31 (69)	8 (38)	23 (51)	14 (31)
Dizziness	2 (8.3)	24 (53)	19 (42)	1 (5)	14 (31)	9 (20)
Disorientation	NR	13 (29)	5 (11)	NR	1 (2)	0
Mood Changes	NR	6 (13)	5 (11)	NR	1 (2)	0
Nausea	3 (12.5)	4 (9)	8 (18)	2 (9.5)	4 (9)	5 (11)
Dysphoria	4 (16.6)	NR	NR	0	NR	NR
Hallucinations	3 (12.5)	NR	NR	0	NR	NR
Headache	0	NR	NR	3 (14)	NR	NR
Drowsiness	0	NR	NR	2 (9.5)	NR	NR
Vomiting	1 (4.2)	NR	NR	1 (5)	NR	NR
Lightheadedness	0	NR	NR	1 (5)	NR	NR
Decreased oxygen saturation	0	NR	NR	1 (5)	NR	NR

	Majidinejad Overall Adverse Events *N* = 126	
	Ketamine *n* = 63	Morphine *n* = 63
Emergence phenomenon	6	0
Rescue medication requests	4	0

Limitations:

Limitations of the study would include the degree of heterogeneity between the groups as suggested by the I square analysis with ~64%, which corresponds to a moderate amount of heterogeneity between these studies, which may not be fitting for a meta analysis. This limits the ability to interpret statistical significance of these studies or to make inferences from the data to support changes in clinical practice. Though the studies also are reported to indicate “non-inferiority” of ketamine to morphine, really the main conclusion would be that morphine is not superior, and with the heterogeneity and small number of studies, there are concerns about the confidence in the conclusions.