CME

A Systematic Review and Meta-analysis of Ketamine as an Alternative to Opioids for Acute Pain in the Emergency Department

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ABSTRACT

Background: Opioids are commonly prescribed in the emergency department (ED) for the treatment of acute pain. Analgesic alternatives are being explored in response to an epidemic of opioid misuse. Low-dose ketamine (LDK) is one opioid alternative for the treatment of acute pain in the ED.

Objectives: This systematic review and meta-analysis sought to quantify whether LDK is an effective and safe opioid alternative for acute pain reduction in adults in the ED setting. (PROSPERO Registration Number CRD42017065303).

Methods: This was a systematic review of randomized controlled trials comparing intravenous opioids to LDK for relief of acute pain in the ED. Studies where the control group initially received opioids prior to ketamine were excluded. A research librarian designed the electronic search strategy. Changes in visual analog scale or numeric rating scale pain scales were analyzed to determine the relative effects of LDK and opioids in the treatment of acute pain.

Results: Three studies met the criteria for inclusion in this meta-analysis. Compared to pain scale reduction with morphine, ketamine was not inferior (relative reduction = 0.42, 95% confidence interval = –0.70 to 1.54). No severe adverse events were reported in any study, but higher rates of nonsevere adverse events were observed with ketamine.

Conclusions: Ketamine is noninferior to morphine for the control of acute pain, indicating that ketamine can be considered as an alternative to opioids for ED short-term pain control.

Acute pain is one of the most common causes of emergency department (ED) presentations with up to 78% of visits including pain as a presenting complaint.[1] Timely, effective, and compassionate pain management is a critical element of patient care, and opioids are one well-accepted, readily available, and time-tested option to treat pain in the ED.[1,2] Despite increasing reliance upon opioids for acute analgesia in the ED, oligoanalgesia is still common, particularly in African Americans and women as well as the young

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and the very old.[3–6] Several ED-based physician research groups, such as the Alternatives to Opioids (ALTO) program and the opioid-free ED program, are investigating methods and the efficacy of reducing ED usage of opioids for certain conditions while also improving overall pain control.[7,8] While the goal is not to completely eliminate the use of opioids as they are useful, safe, and effective in the correct patient populations, demonstrating that these alternative analgesics are comparable to opioids is important if they are to be used, particularly if used as a replacement for opioids.

Ketamine, one compelling opioid alternative, is a noncompetitive antagonist of *N*-methyl-D-aspartate receptors in the central nervous system. ED physicians safely administer ketamine for procedural sedations and intubation as well as prehospital agitation.[9–12] Subdissociative-dose ketamine refers to intravenous (IV) administration of ketamine at doses of ≤0.5 mg/kg.[13] As patients can still become dissociated or have psychiatric complaints, we shall instead refer to this as low-dose ketamine (LDK). Two previously conducted reviews[14,15] evaluating LDK in the ED suffered significant limitations by including pediatric trials,[16] trials where ketamine was administered with other analgesics,[17,18] and patients where ketamine was administered for procedural sedation[17] leaving the independent effect of ketamine on acute pain control unresolved.

Our primary objective was to quantify the short-term (≤60 minutes) analgesic efficacy of LDK, administered as an initial one-dose, single-agent IV bolus in adults between 18 and 65 years of age in the ED via a systematic review and meta-analysis. The decision to impose strict requirements provides this review additional accuracy as compared with prior reviews[14,15] that could neither isolate effects of different routes of administration or the potential biases of noncontrolled studies. The secondary objective was to quantify the risk of adverse effects attributable to ketamine used as an opioid alternative for ED analgesia.

METHODS

Study Design

This systematic review and meta-analysis is registered in the PROSPERO International Prospective Register of Systematic Reviews (Registration Number CRD42017065303) and conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines and checklist.[19,20]

Search Strategy

A medical librarian designed and conducted the electronic search strategy using a combination of standardized terms and key words, in Ovid Medline 1946-, Embase 1947-, Scopus 1960-, Database of Abstracts of Reviews of Effects, and Cochrane Database of Systematic Reviews as well as in the gray literature databases Cochrane Central Register of Controlled Trials, Clinicaltrials.gov, and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). All searches were completed in February 2017. A study-type filter for randomized controlled trial (RCT) was used. Results were exported to EndNote. The automatic duplicate finder in EndNote was used, and then the results were manually searched for duplicates. Full search strategies are provided in the supplemental materials.

Eligibility Criteria

Eligible trials met the following criteria: 1) RCTs; 2) compared the analgesic effect of IV LDK (≤0.5 mg/kg/dose administered as a bolus, slow push, or short infusion) in patients with acute pain to IV opioids, which was then converted to morphine equivalent dosing with a primary outcome of change in either the visual analog scale (VAS) score or numeric rating scale (NRS) pain scale from baseline to a second pain score within 60 minutes of intervention; 3) ED setting; 4) enrolled adult (≥18 years old) patients presenting with acute pain; and 5) were published in English. Acute pain was defined as pain beginning within the previous week that was a presenting ED complaint, including both traumatic and nontraumatic sources. Only studies where both the intervention and the active comparator were administered intravenously were included because the pharmacokinetics and therapeutic effects of either ketamine or opioids change based on its route of administration (i.e., intranasal, intramuscular).[21] Given the differing usage and effect of ketamine in pediatric populations, we limited our study to adults.[22]

Exclusion criteria included: 1) did not report VAS or NRS pain scores; 2) protocol contained a coadministration of a phamacologically active substance less than 20 minutes after IV ketamine/opioid administration; or 3) included a placebo comparison group. As drug–drug interactions of ketamine and other sedatives and analgesics are complex, trials with coadministration of another pharmacologically active analgesic medication in either the intervention or the control group

were excluded. The current standard of care for severe acute pain includes the administration of analgesia, including opioids, so trials with a placebo comparison group were excluded.[23–25]

Data Extraction

Two reviewers independently screened the identified citations by title and abstract for exclusion. Manuscripts of all remaining citations were retrieved electronically and subject to full-text review with further exclusions made. The references of all included manuscripts were reviewed for additional relevant citations. Any disagreements were resolved by discussion between independent reviewers and, if necessary, through consultation with an additional adjudicator. We contacted any author where details of mean or median change in pain score was not readily available and used provided data to calculate primary outcome measures as detailed in the supplemental materials. Secondary outcomes included adverse events and the requirement of additional dosing or analgesics.

For eligible RCTs the following data were abstracted: 1) journal name, author(s), year of publication; 2) subject recruitment inclusion criteria and exclusion criteria; 3) sample size in each trial arm, subject age ranges and/or means, sex distributions, country and city in which trial was conducted; 4) IV dosage of ketamine/opioid (mg/kg) in each trial arm; and 5) baseline and any postintervention VAS/NRS pain scores reported, including all means, mean changes, standard deviations (SDs), and standard errors reported for any time point less than 120 minutes after intervention administration; and 6) all reported data pertaining to adverse event rates, inadequate analgesia, and additional analgesic medications requests.

Our primary outcome was the difference in pain scores after the administration of ketamine or an opioid from baseline to a reported time point closest to 10 minutes after administration. Pain assessments used either the VAS or NRS. Our a priori primary outcome was both the mean and the SD or standard error of the change in VAS/NRS score from baseline to a specific second time point reported closest to 10 minutes postintervention. The mean instead of the median value was chosen as we were unable to obtain enough information from all the included studies to calculate the median but had enough information to calculate the mean values for all included studies. This decision was made in consultation with two of the authors who teach advanced statistics and study methodology. We chose 10 minutes for the comparison point because it was found to be a common reported time point for acute pain relief between opioid and ketamine trials. We anticipated varied data formats and accordingly extracted all related data reported by each individual trial less than 120 minutes after intervention with the intention of calculating our specific desired outcome measures. If this were not possible for a specific trial, authors were contacted directly to request deidentified individual subject pain scores to allow for direct calculation.

We did not define adverse events for our secondary outcomes. Instead, we abstracted all adverse events reported as well as measures of inadequate analgesia from each trial.

Risk of Bias Assessment

The quality and risk of bias of included studies were assessed according to guidelines provided in the Cochrane Handbook of Systematic Reviews of Interventions.[26] Once studies were determined to fit the inclusion criteria, additional data were extracted for each study to specifically assess for adequate random sequence generation, allocation concealment, subject blinding, outcome blinding, and procedures for dealing with incomplete data and selective reporting. We intended to test publication bias with a funnel plot.[27]

Data Analysis

Primary outcome data were analyzed using STATA/IC 14.1. METAN and METAFUNNEL routines were employed to perform random effects meta-analysis and publication bias assessments, respectively. The random-effects model was chosen because the expected heterogeneity among included studies would likely lead to varied true effect size between trials.[28] Trial heterogeneity was evaluated by I^2 and chi-square tests.[29] For the primary outcome measure, we pooled the difference in the change in VAS/NRS scores from baseline to a second time point between the ketamine and opioid trial arms and reported 95% confidence intervals (CIs) for this comparison. If studies reported adverse effects incidence data resulting from the included interventions, secondary outcome data were meta-analyzed; however, we preplanned relatively few analyses because of the expected variation in the format of secondary outcome data reports between trials. When secondary outcome data had a consistent format, a meta-analysis was performed in the scale of this specific format.

However, if data were not sufficiently available for meta-analysis, a qualitative synthesis was performed and reported.

A sensitivity analysis was performed in which the meta-analysis was rerun twice to ensure results would be comparable with either more or less stringent inclusion criteria. The CI of the mean change in pain scale score defined the level of heterogeneity. The first sensitivity analysis was done including the most homogenous excluded trial, Gurnani et al.,[30] and the second was performed through the exclusion of the most heterogeneous included trial, Majidinejad et al.[31]

RESULTS

The literature search described in Figure 1 resulted in three trials that met the inclusion and exclusion criteria.[31–33] The three RCTs included a total of 261 patients. Figure S1 in Data Supplement S1 (available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13502/full) provides a full breakdown of rejected citations. The dosing of ketamine was similar among the studies and all three used the same dosing regimen of morphine. Two of the three trials occurred in the United States, and one took place in Iran. In each study, either a clinician or a trained researcher was responsible for conducting the NRS pain scale evaluation. The studies are further described in Table 1.

Quality Assessment

The studies were low risk for allocation concealment, blinding of outcome, blinding of participants and personnel, and selective reporting. Random sequence generations was low risk for Motov and of unclear risk for Majidinejad and Miller. Incomplete outcome data was of unclear risk for Majidinejad and low risk for the rest.

Primary Outcome Data Analysis

We contacted all authors, and we were able to use patient level data or reported values to calculate the standard error in the change of pain scales. Motov and Miller shared deidentified individual subject pain scores at all collected time points. This allowed us to directly calculate the standard error of change in NRS pain scores for these two trials (see supplemental materials for reported and calculated values). None of the trials demonstrated a clinically significant difference between reduction in pain scores between ketamine and morphine (Table 2).

Effect estimates and standard errors were input directly into STATA, and the METAN procedure was used to perform a random effects meta-analysis of the change in pain scores from baseline to postintervention between trial arms (Figure 2). The pooled estimate of the mean change in pain scores between the ketamine and morphine arms was 0.42 (95% CI = –0.70 to 1.54) where positive values suggest ketamine was superior to morphine in reducing pain. The CI does not suggest that morphine is clinically superior to ketamine for analgesia. The pooled CI for the difference in effect between ketamine and morphine for all included studies does not contain any value less than –1.4 with ±1.4 being the margin of clinical significance and negative values favoring morphine. Thus, ketamine was statistically noninferior to morphine as an analgesic in this meta-analysis.

Sensitivity Analyses

The first sensitivity analysis was intended to be performed by including one of the excluded trials. The trial was chosen as it had the least number of reasons to be excluded compared to the rest of the excluded studies. Gurnani et al.[30] was excluded because the article only reported a graph of pain changes but not the numerical values. We were unsuccessful in our attempts to make contact with the authors to obtain the values. Therefore, we could not perform this sensitivity analysis beyond visual comparison of the reported graph that indicated LDK had a greater effect at 15 minutes ($p < 0.05$) than morphine.[30]

The second preplanned sensitivity analysis removed the most heterogeneous trial included in the meta-analysis, the Majidinejad trial, to ensure that the inclusion criteria were not too broad to bias the data. As with the reported data in Table 1, Majidinejad differed from the Motov and Miller trials in location, ketamine dosing, and included indications. We repeated our primary outcome meta-analysis without including the effect estimates of the Majidinejad trial (Data Supplement S2, Figure S2, available as supporting information in the online version of this paper, which is available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13502/full). This second sensitivity analysis produced a point estimate for reduction in NRS pain score of 1.04 (95% CI = 0.09 to 1.99), favoring the effectiveness of ketamine. This is similar to the overall results of the review that found a point

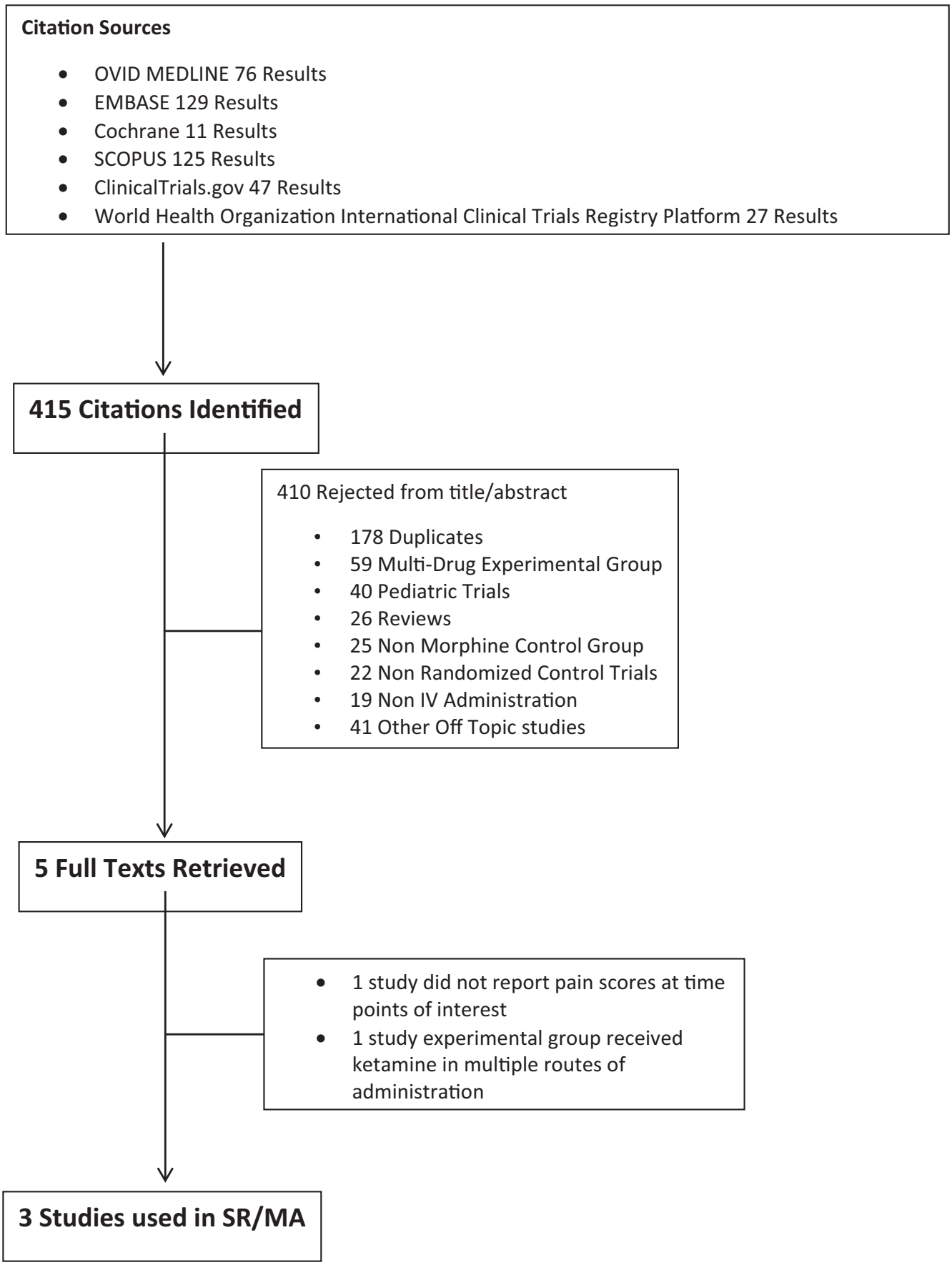

Figure 1. Flow diagram of studies identified and included. SR/MA = systematic review/meta-analysis.

Table 1
Trials Included in the Meta-analysis

Study	Sample Size	Follow-up Period (Minutes)	Location	Sex Distribution (% Male)	Age Range, Mean Age (Years)	Effect Estimate ($\Delta Mean_{K-M}$)	Included Indications	Intervention (Ketamine Dosing)	Control (Morphine Dosing)	Pain Scale	Adverse Events Reported?
Majidinejad, 2014[31]	126	10	Isfahan, Iran	76%	18–55, 33.6 ± 14.3 morphine 35 ± 13.5 ketamine	–0.45	Long-bone fractures	IV 0.5 mg/kg	IV 0.1 mg/kg	NRS	Y
Miller, 2014[32]	45	120	San Antonio, TX	36%	18–59, 30	0.82	Acute abdominal, flank, or musculoskeletal pain	IV 0.3 mg/kg	IV 0.1 mg/kg	NRS	Y
Motov, 2015[33]	90	120	New York, NY	51%	18–55, 35	1.20	Acute abdominal, flank, or musculoskeletal pain	IV 0.3 mg/kg	IV 0.1 mg/kg	NRS	Y

The data for the Majidinejad trial age range was broken down further because of the discrepancy in reporting of mean age between the two trial arms within the article.
NRS = Numeric Rating Scale; Y = yes.

estimate for the reduction of NRS pain score of 0.42 (95% CI = –0.70 to 1.54) favoring ketamine. While the second analysis favored ketamine, it fell below the clinically significant difference of 1.4.

Assessment of Publication Bias

A funnel plot analysis was performed; however, after visual inspection, it was not included as it could not properly assess for bias due to the limited number of included studies.

Secondary Outcome

Due to the very different manner and degree of adverse event and rescue medication reporting between included trials, a meta-analysis or other quantitative synthesis was not possible (Table 3). Majidinejad reported the fewest categories of adverse events and only followed patients for 10 minutes after receiving the study medication. It was not clear what overlap, if any, existed between these two categories, so an overall adverse event rate was not calculated. In contrast, Motov and Miller followed patients for 2 hours after medication administration. Motov identified adverse events at 15, 30, 60, 90, and 120 minutes. Miller reported overall event rates without identifying when they occurred during the trial. Additionally, Miller reported several categories not reported in the other two trials.

DISCUSSION

Ketamine is a safe, effective alternative to opioids in the treatment of acute pain in the ED. By restricting many potential confounding variables with our strict inclusion criteria and performing sensitivity analyses, our meta-analysis determined LDK was as effective as opioids at treating acute pain. Prior trials and systemic reviews included patients receiving both ketamine and opioids because ketamine is often used as an adjunct to opioids but this also confounds their results when making a direct comparison between the two. While adverse events associated with ketamine were reported, few appeared to be clinically significant.

Even though there are multiple observation trials studying ketamine,[34–42] the literature supporting it as an alternative to opioids for the management of acute pain is limited by the low quality of study design and small numbers of studies, although newer studies are overcoming these issues.[43] In many instances, the inclusion criteria were either very broad and included

patients that probably should not have received either an opioid or ketamine[44] or compared ketamine to a placebo, a questionable study design considering we have effective analgesics.[23–25] Moving forward, observational studies assessing adverse events should use similar outcome measures and time frames, and researchers should explore patient and physician satisfaction with ketamine analgesia and side effects compared to other opioid alternatives for acute pain.

While our conclusion is limited due to the inclusion of only three studies, our results are consistent with other systematic reviews with broader inclusion criteria. Sin et al.[14] included four RCTs, three of which we excluded, for a total of 428 patients in their review. Of the four studies included, two showed a benefit in pain and distress with ketamine, while the others demonstrated either no difference between ketamine and fentanyl or ketamine and a placebo. In another meta-analysis that also included trials we excluded, Lee and Lee[15] included six trials and 438 patients and found ketamine to be either similar or superior to opioids and placebos. Ketamine was associated with a higher rate of neurologic and psychiatric adverse events (respectively, RR = 2.17, 95% CI = 1.37 to 3.42, $p < 0.001$, NNH = 9; RR = 13.86, 95% CI = 4.85 to 39.58, $p < 0.001$, NNH = 4), while opioids were associated with a higher risk of major cardiovascular events (RR = 0.22, 95% CI = 0.05–1.01, $p = 0.05$, NNH = 28), although the clinical significance of this is debatable.

Understanding the limitations of existing research, the general acceptance and widespread implementation of ketamine as an analgesic in the ED is surprising[45] and may in part be due to emergency physicians' familiarity with ketamine. Additionally, multiple free online access to medical education movement sites and blogs publicized ketamine as an alternative to opioids,[46–49] and the American College of Emergency Physicians (ACEP) lists ketamine as an alternative to opioids thereby also increasing its credibility.[50] While alternative analgesics such as ketamine continue to grow in popularity, the purpose of this article is not to argue that ketamine should replace opioids in the ED. In fact, there is most definitely a role for opioids in

Table 2
Mean Difference in NRS Score

Trial Number	Author	Year	$n_{Ketamine}$	$n_{Morphine}$	$\Delta NRS\ Mean_{K-M}$	Pooled SE
1	Majidinejad	2014	63	63	–0.45	0.414
2	Miller	2014	24	21	0.82	0.745
3	Motov	2015	45	45	1.20	0.638

The absolute value of the change in the morphine arm was subtracted from the absolute value of the change in the ketamine arm. The precise effect estimates and standard errors of the change from baseline to postintervention NRS scores for all included trials are not clinically significantly different in any trial.
NRS = numeric rating scale; SE = standard error of each sample distribution.

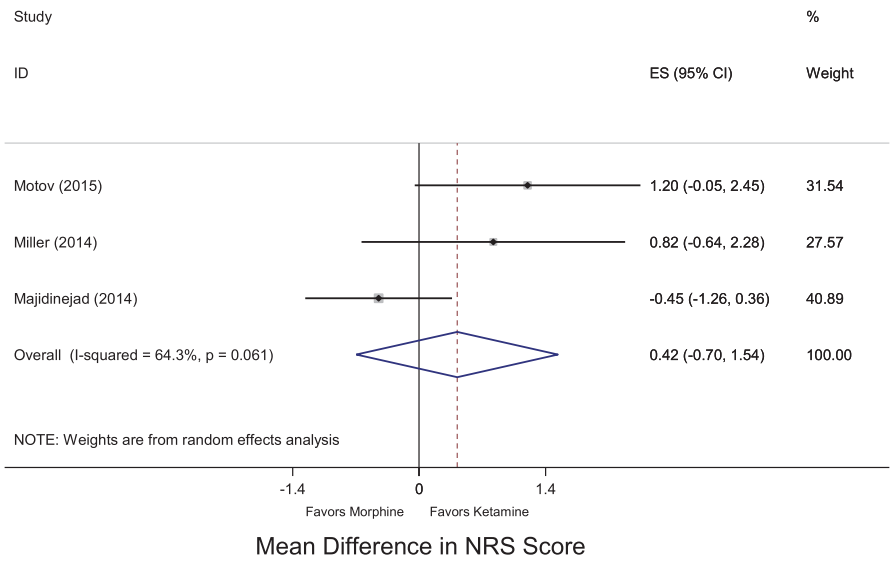

Figure 2. Forest plot of mean change in pain rating for morphine compared with ketamine. Analysis of the three included papers indicated no clinically significant inferiority of ketamine compared to morphine.

Table 3
Adverse Events in the Included Trials

	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
Numbness	1 (4.2)	NR	NR	0	NR	NR
Pruritus	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

All data are reported as a raw count (n) as well as a percentage of patients (%) within each trial arm. Miller and Motov broke down the time points of adverse events differently with Miller reporting a total count across the two hour study and Motov breaking down adverse events at time of medication and after 15 minutes.
N = sample size; n = trial arm size; NR = not reported; t = time.

the treatment of pain in the ED. However, we do believe that it is important to establish that alternatives such as ketamine are comparable to opioids so that if a clinician decides to order it instead, they can be confident that the patient obtains appropriate analgesia in a comparable time frame. We feel this is important as physicians continue to face pressure to reduce their opioid use. Additionally, a policy statement released by ACEP suggests that ketamine can be administered as a monotherapy, even more reason to make sure it provides equivalent analgesia to opioids.[51]

For patients with opioid use disorders or substance use disorders that require a potent analgesic in the ED such as a narcotic, ketamine may be a favorable option compared to an opioid. While there is some recent evidence demonstrating addiction being associated with receiving an opioid prescription from the ED,[52] there is not evidence demonstrating that receiving a single dose or even a few doses of an opioid in the ED is associated with the development of an opioid use disorder.[52,53] While the known addictive properties of opioids drove research to find alternative medications, ketamine is also potentially addictive and abuse has been reported.[54–56]

Beyond concerns of post-ED misuse or addiction potential, there are additional reasons to consider ketamine as an alternative analgesic. Opioids are associated with adverse events such as nausea, vomiting, pruritus, hypotension, respiratory depression, and hypoxia.[57–59] In the elderly or patients with chronic pulmonary disease, the treating physician may be hesitant to administer opioids due to concerns for respiratory depression.[60–62] Some opioids can "stack" in patients with renal failure causing delayed respiratory depression and failure.[63] Ketamine may be preferable in such patients to reduce respiratory complications. However, ketamine is also associated with several adverse effects including laryngospasm, nausea and vomiting, and emergence reactions. Additionally, ketamine is hepatically cleared and dosage adjustment is necessary for patients with hepatic impairment.[64] The adverse event rates in the studies included in this review are consistent with previous research,[65] namely, that ketamine has lesser risk of severe adverse reactions than morphine, but a greater risk of emergence phenomenon and dizziness. New research indicates that a short infusion of LDK compared to a push dose is associated with fewer psychiatric adverse effects and

less sedation.[43] Another less well-known associated adverse event from ketamine is the development of lower urinary tract symptoms (LUTS) such as frequency, urgency, and dysuria as well as the possibility of renal failure.[66] Importantly, LUTS seem to improve with cessation of use.[67] While LUTS were once thought to only occur with chronic ketamine exposure, it is now associated with even infrequent use.[66] This could be important to consider for patients repeatedly presenting to the ED with a painful condition requiring an analgesic.

LIMITATIONS

More liberal inclusion criteria may have changed our results. Our strict selection criteria allows us to be sure that our effect estimates are attributed to ketamine and morphine alone, rather than potential additive or synergistic interactions with other agents, although it may decrease the generalizability of our results. We believe that by being more stringent that we were better able to compare ketamine to opioids. As with any systematic review, missed studies may have influenced our results. However, a medical research librarian performed our stringent search strategy and we identified an additional study that was not included in any previous review. We did not calculate a kappa inter-rater reliability with the eligibility and selection process as the two reviewers were in full agreement. Finally, while we attempted to contact all authors of included trials, we were unable to reach one author limiting our ability to include their data in a meta-analysis.

CONCLUSION

Intravenous ketamine is noninferior to intravenous morphine in the control of acute pain in adults in the ED. Severe side effects were absent in both arms, but side effect profiles of LDK and opioids differed.

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Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13502/full

Data Supplement S1. Methods supplement.

Data Supplement S2. Results supplement.