Critical Review Form
Therapy

Motov S, Rockoff B, Cohen V, et al. Intravenous Subdissociative-Dose Ketamine Versus Morphine for Analgesia in the Emergency Department: A Randomized Controlled Trial. Ann Emerg Med. 2015 Sep;66(3):222-229.e1.

Objectives: **To test the hypothesis "that a subdissociative dose of ketamine administered as a single agent at 0.3 mg/kg will provide relief similar to that of a standard dose of morphine at 0.1 mg/kg for acute moderate to severe pain in the ED setting." (p. 223)**

Methods: **This prospective, randomized, double blind controlled trial was conducted using a convenience sample of patients enrolled between June 2013 and May 2014 in the ED at Maimonides Medical Center in Brooklyn, NY. Patients aged 18 to 55 years with acute abdominal, flank, back, or musculoskeletal pain with a pain score of 5 or more on an 11-point numeric scale presenting to the ED at a time when both a study investigator and the ED pharmacist were available were eligible for enrollment. Exclusion criteria included pregnancy, breast-feeding, altered mental status, allergy to one of the study drugs, weight less than 56 kg or more than 115 kg, unstable vital signs, acute head or eye injury, chronic pain, hepatic or renal insufficiency, alcohol or drug abuse, psychiatric illness, or opioid use within the last 4 hours.**

Patients were randomized in a 1:1 fashion to receive either IV morphine (0.1 mg/kg) or IV ketamine (0.3 mg/kg). Pain was then recorded at 15, 30, 60, 90, and 120 minutes. If any pain score was 5 or more, a rescue dose of fentanyl (1 mcg/kg) was administered) IV. The primary outcome was the reduction in the numeric rating scale pain at 30 minutes after injection of the study medication. Secondary outcomes included the need for rescue medication at either 30 or 60 minutes, vital sign changes and adverse events.

There were 90 patients enrolled in the study (45 in the ketamine group, 45 in the morphine group). The mean ages were 35 and 36 respectively, and 67% and 62% were women.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. Patients were randomized at a 1:1 ratio using blocks of 10 participants (up to 90).

2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Likely yes. "ED pharmacy investigators maintained the randomization list, which was generated before commencement of the study, prepared the medication, and delivered it to the nurse caring for the study participant in a blinded manner." (p. 223)
3.	Were patients analyzed in the groups to which they were randomized?	Yes. The patients were analyzed according to which drug they were initially randomized to receive (intention to treat analysis). The authors do not mention any crossover in the study).
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, weight, initial vital signs, cause of paint, and baseline degree of pain on the numeric pain rating scale.
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No. " The preparing pharmacist, research manager, and statistician were the only members of the team with knowledge of the study arm to which the participant was randomized, leaving the providers, participants, and data- collecting research team blinded to the medication received." (p. 224)
2.	Were clinicians aware of group allocation?	No. See above.
3.	Were outcome assessors aware of group allocation?	No. See above.
4.	Was follow-up complete?	Mostly yes. Complete follow-up data was available in all patients for the final outcome (pain improvement at 30 minutes). For 60-minute and 90-minute outcomes, 2 patients in each group were lost to follow-up. At 120 minutes, there were 4 patients lost to follow-up in the ketamine group and 3 lost to follow-up in the morphine group.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• Both groups of patients had significant reductions in pain score at all time points. • At 15 minutes, the mean difference in pain score was –1.0 (95% CI –2.40 to 0.31) in

		favor of morphine. • At 30 minutes, the primary outcome comparison, the mean difference, was 0.2 (95% CI –1.19 to 1.46) in favor of ketamine. • At 60, 90, and 120 minutes, pain scores were slightly lower in the ketamine group, with no statistically significant difference. • The number of patients with "Complete resolution of pain" at 15 minutes was higher in the ketamine group (44% vs. 13%; absolute difference 31%, 95% CI 13.1% to 49.2%). There was no significant difference at any other time point. • While there was no significant difference in the proportion of patients requiring rescue analgesia (IV fentanyl) at 30 or 60 minutes, the proportion was significantly higher in the ketamine group at 120 minutes (absolute difference 17%; 95% CI 1% to 34%). • No serious or life-threatening adverse events occurred in either group and there were no clinically concerning changes in vital signs. • A significantly higher proportion of patients in the ketamine group reported any adverse effects after medication injection (absolute difference 38%; 95% CI 18% to 57%).
2.	How precise was the estimate of the treatment effect?	See above. This was a relatively small study with wide confidence intervals.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes. These were ED patients in the US presenting with acute abdominal, back, flank, or musculoskeletal pain. Given the extensive list of exclusion criteria, it is not generalizable to all patients presenting with pain, and care must be taken to apply the results of this study to appropriate patient population (young and relatively healthy nonpregnant patients).
2.	Were all clinically important outcomes considered?	No. The authors did address pain out to 2 hours following drug injection, but did not evaluate patient satisfaction, ED length of stay, or cost.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. In this relatively small study, ketamine did not provide any benefit in terms of pain score reduction at 30 minutes (the primary

		outcome), or at 15, 60, 90, or 120 minutes. There were, however, a higher proportion of patients reporting initial adverse effects and a higher proportion of patients requiring rescue analgesia with IV fentanyl. While ketamine appears relatively safe in the management of acute pain in select patients in the ED meeting strict inclusion criteria, it's use may be limited by these increases in adverse effects and need for rescue medication.

Limitations:

1. **The authors did not assess several important outcomes, including ED length of stay and patient satisfaction.**
2. **There were 7 of 90 patients (7.8%) without complete, 2-hour follow-up data.**
3. **A convenience sample of patients was enrolled when study investigators and pharmacists were available.**
4. **Extensive inclusion and exclusion criteria were used, limiting the generalizability of the results to patients for whom we might be interested in using ketamine as an alternative to opiates (i.e. elderly patients or those with unstable vital signs) (external validity).**

Bottom Line:

This small, randomized, double blind controlled trial demonstrated no significant difference in the reduction in the numeric rating scale pain at 30 minutes after injection of morphine vs. ketamine. The number of patients with "Complete resolution of pain" at 15 minutes was higher in the ketamine group, but this difference was not present at other time points. By two hours after injection, more patients in the ketamine group required rescue analgesia than in the morphine group, with more adverse effects reported among those receiving ketamine. These results suggest no benefit to administering ketamine over morphine, with an increased need for rescue analgesia and higher rate of adverse effects.