Critical Review Form
Therapy

Beaudoin FL, Lin C, Guan W, Merchant RC. Low-dose ketamine improves pain relief in patients receiving intravenous opioids for acute pain in the emergency department: results of a randomized, double-blind, clinical trial. Acad Emerg Med. 2014 Nov;21(11):1193-202.

Objectives: **"to determine the comparative effectiveness of low doses of ketamine as an adjunct to morphine versus standard care (morphine alone) for the treatment of acute severe pain among patients presenting to the ED." (p. 1195)**

Methods: **This placebo-controlled, double-blind, randomized controlled trial was conducted at the Rhode Island Hospital ED from December 2012 through September 2013. A convenience sample of patients was recruited during scheduled 8-hour times blocks, Monday through Saturday between 8 AM and 12 AM. English-speaking patients, aged 18 to 65 years old, with moderate to severe acute pain (score of ≥ 5 out of 10 on the numerical pain rating scale [NRS] for < 7 days), deemed by the treating clinician to require IV opioid analgesia, were eligible for inclusion. Patients with neurologic, respiratory, or hemodynamic compromise; with known or suspected allergy to ketamine or morphine; with acute psychiatric illness, history of stroke, renal impairment, liver failure, history of cardiac disease, or who were pregnant or breastfeeding, were excluded.**

Patients were randomly assigned to one of three groups: 1) Patients in the standard care group received morphine and 0.9% saline placebo; 2) Patients in group 1 received morphine and 0.15 mg/kg of IV ketamine; 3) Patients in group 2 received morphine and 0.3 mg/kg of IV ketamine. All patients were given 0.1 mg/kg of IV morphine (up to 10 mg) initially. Additional rescue analgesia was provided at the discretion of the treating physician at a dose of 0.05-0.1 mg/kg of IV morphine, administered as frequently as every hour.

The primary outcome was pain relief, as measured using the summed pain-intensity difference (SPID) over 2 hours (Farrar 2000). Patients whose %SPID (percentage of maximum achievable SPID) was at least 33% were considered to be treatment responders. Secondary outcomes included NRS measurements at each time point (0, 30, 60, and 120 minutes), total patient-perceived pain relief, amount of rescue analgesia received, time to rescue analgesia, global analgesic effectiveness (a combination score of SPID and rescue analgesia), and adverse events.

There were 69 patients initially randomized, of whom 9 were withdrawn prior to receiving study medication, leaving 20 patients in each group.

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. "each participant enrolled in the study was randomly assigned to one of three study groups using a computer-generated block randomization schedule with block sizes of six." (p. 1195)
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?	Yes. Computer-generated block randomization was used, and should sufficiently maintain allocation concealment, and randomization, allocation, and dispensing of medication were overseen by a hospital pharmacist who was not involved with any other aspect of the study. Patients received equal volumes of study medication (0.1 mL/kg) or placebo to maintain allocation concealment.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. Patients were analyzed using an intention to treat analysis. The authors do not mention any crossover within the study.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Somewhat. While there were no statistically significant differences in baseline characteristics between the groups, there were some clinically significant differences that did not achieve statistical significance because of the small sample sizes. For example, there was a significantly higher proportion of female patients in Group 2 (55%) compared to the Standard Care Group (25), there were twice as many patients with chronic pain (30% vs. 15%) and three times as many patients with opioid use in the last 24 hours (30% vs. 10%) in Group 1 compared to the Standard Care group. There were five times as many patients with a fracture in the Standard Care Group vs. Group 1 (25% vs. 5%).
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, "participants, providers, RAs, and study investigators were blinded to group allocation."

2.	Were clinicians aware of group allocation?	No.
	Were outcome assessors aware of group allocation?	No.
4.	Was follow-up complete?	No. There were 4 patients (20%) with missing data at 2 hours.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• The median change in pain intensity score at each time point was ≥ 2 for all treatment groups. • SPID scores were higher in both Group 1 and Group 2 compared to the Standard Care Group (7.0, 7.8, and 4.0 respectively). • %SPID was significantly higher Group 1 and Group 2 compared to the Standard Care Group (39%, 42%, and 21% respectively). • The percent of patients with a %SPID of at least 33% was higher in Group 1 and Group 2 compared to the Standard Care Group (50%, 70%, and 25% respectively). • There was no statistically significant difference between the standard care group and Group1 and Group 2 with regards to the use of rescue analgesia (35%, 20%, 20% respectively, $p = 0.48$). • There was no statistically significant difference in the median amount of analgesia administered to those requiring rescue analgesia between the standard care group, Group 1, and Group 1 (6.1 mg, 5.4 mg, and 4.3 mg; $p < 0.53$). • There was a higher rate of dizziness or lightheadedness at 30 minutes in Group 2 compared with the other two groups. There no patients in the standard care group, 2 in group 1, and 3 in group 2 reporting significant dysphoria. • Median length of stay was shorter in the standard care group (135.5 minutes) than either Group 1 (170 minutes) and Group 2 (172.5 minutes). While this did not achieve statistically significant difference, there is a clearly clinically important difference.
2.	How precise was the estimate of the treatment effect?	95% Confidence intervals were not provided, and there is insufficient data to do so.
III.	**How can I apply the**	

	results to patient care (answer the questions posed below)?	
1.	Were the study patients similar to my patient?	Likely yes. This study was conducted at a large, Level 1, tertiary care emergency department in the US and comprised a broad range of pain disorders. This is likely similar to what we see at our institution.
2.	Were all clinically important outcomes considered?	No. The authors did not address cost, or long-term pain control. These would be very important outcomes to consider, as differences in these outcomes may negate the benefits reported.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This was a very small study, and while the numbers indicate an overall improvement in pain in the first 2 hours with the administration of ketamine, there are several issues to consider. 1) Patients in the standard care group did not receive more IV morphine than the other two groups, despite having higher reported pain scores, suggesting they were underdosed 2) The study enrolled a wide range of patients with acute pain with a very subjective threshold for enrollment based on the NRS score. Patients with acute fracture were therefore enrolled and studied alongside patients with such benign diseases as dental pain. 3) The authors do not address important outcomes, such as ED length of stay, the results of which could negate any benefit observed.

Limitations:

1. **This was a very small study, and while statistically significant differences in baseline characteristics were not seen, clinically significant differences were observed.**

2. **There was no statistically significant in the percent of patients given rescue analgesia, or in the amount of rescue analgesia given between the groups. This suggests that perhaps underdosing of morphine in the standard care group resulted in less improvement in the NRS score, rather than the administration of ketamine.**

3. **While the p-values for comparing Groups 1 and 2 with the standard care group for the primary outcomes were < 0.05, this is a poor marker of either clinically**

meaningful or statistically meaningful difference. The interquartile ranges (IQRs) overlap between all three groups for these outcomes.

4. **Loss to follow-up was relative high given the small sample sizes; 20% of patients did not have complete outcome data.**

<u>Bottom Line:</u>

This small, double-blinded randomized, controlled trial demonstrated improved pain scores at 2 hours in patients receiving ketamine and morphine compared to those receiving morphine alone. The application of these results is limited by the lack of additional clinically important outcomes (long-term pain control), the high rate of dysphoria associated with ketamine (10% and 15% in groups 1 and 2 respectively), the increase in ED length of stay in those patients receiving ketamine, and the broad range of clinical entities enrolled, including dental pain.