Critical Review Form
Therapy

Galinski M, Dolveck F, Combes X, Limoges V, Smaïl N, Pommier V, Templier F, Catineau J, Lapostolle F, Adnet F. Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. Am J Emerg Med. 2007 May;25(4):385-90.

Objectives: **to test "the hypothesis that the combination of small- dose ketamine and morphine would promptly reduce pain perception and morphine consumption compared with morphine alone in trauma patients with severe acute pain in emergency settings." (p. 386)**

Methods: **This prospective, multicenter, randomized double-blind, controlled study was conducted at five emergency departments using mobile intensive care units in France between January 1, 2003 and January 31, 2005. Patients with trauma and a "severe acute pain,' defined as visual analog scale (VAS) score of at least 60 out of 100; aged 18 to 70 years; without acute respiratory, neurologic, or hemodynamic compromise, were eligible for inclusion. Patients with a psychiatric history; chronic respiratory, renal, or hepatic failure; known allergy to ketamine; known opioid allergy; chronic pain being treated with opioids; pregnancy; inability to understand the VAS score; or an indication for local or regional analgesia were excluded, as were patients who had already received an opioid analgesic for their acute pain.**

Patients were randomly allocated to receive either morphine (0.1 mg/kg) and ketamine (0.2 mg/kg) (the K group) or morphine (0.1 mg/kg) and placebo (the P group). IV morphine was administered and titrated to pain score. The primary outcomes were the VAS score and amount of morphine administered at 30 minutes. The VAS score was assessed initially, then every 5 minutes until their arrival at the hospital, and was recorded at 0, 15, and 30 minutes. All vital signs, the level of sedation measured by the Ramsay Score, and adverse effects were recorded.

A total of 73 patients were enrolled in the study, 7 of whom were withdrawn because of incomplete data or failure to follow study protocol. One additional patient was excluded following an anaphylactoid reaction to an antibiotic injection, leaving 65 patients in the final analysis. There were 33 patients in the K group and 32 in the P 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. "A table of random numbers determined the randomization sequence, using a restricted randomization scheme to ensure roughly equal numbers in each group." (p. 386)
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. "Group assignments were sealed in opaque envelopes and opened sequentially by the investigators." (p. 386) "Ketamine and placebo were administered from syringes of similar appearances prepared by a nurse anesthetist who was otherwise not involved in the study." (p. 386)
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?	Yes. Patients were similar with respect to age, gender, BMI, trauma etiology, and initial VAS score.
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. This study was blinded via the use of placebo control. Ketamine and placebo were administered from similarly appearing syringes.
2.	Were clinicians aware of group allocation?	No. This study was blinded via the use of placebo control. Ketamine and placebo were administered from similarly appearing syringes.
3.	Were outcome assessors aware of group allocation?	No. "An independent physician-observer blinded to the analgesic treatment group did all assessments of patients." (p. 386)
4.	Was follow-up complete?	Likely yes. The authors do not specifically mention

		loos to follow-up, but presumably all patients remained with the mobile ICU for the full 30 minutes of the study period. There was no long-term follow-up.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• Morphine consumption at 30 minutes was significantly higher in the P group compared to the K group: 0.202 mg/kg vs. 0.149 mg/kg, $p < 0.001$. This required more morphine boluses in the P group vs. the K group: 2.3 vs. 1.0, $p < 0.0001$. • The mean VAS score was similar between the two groups at 30 minutes: 34.1 in the K group and 39.5 in the P group. This difference was not statistically significance. • The proportion of patients reporting excellent satisfaction was similar between the groups: 18% in the K group vs. 22% in the P group, $p = 0.3$. • Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation) were not significantly difference between the groups at 0 or 30 minutes. • The incidence of neuropsychological adverse effects was greater in the K group compared to the P group: 36% vs. 3%, $p = 0.002$. Hallucinations occurred in 4 patients in the K group, dizziness in 6 patients, diplopia in 2 patients, and dysphoria in 6 patients.
2.	How precise was the estimate of the treatment effect?	95% Confidence Intervals were not provided.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	No. These were patients treated in a physician-manned EMS system using a mobile ICU, rather than in the ED itself. Patients were not followed beyond the pre-hospital period. Details of the hospitals to which patients were transported were not provided, nor were the presence of medical comorbidities. In general, however, these were patients suffering acute traumatic injury (largely fractures) and are likely similar to many patients we see suffering blunt trauma or burns.
2.	Were all clinically important	No. This study looked at very short-term outcomes,

	outcomes considered?	including pain level and patient satisfaction at 30 minutes. They did not assess pain control into the ED visit, long-term pain control, ED length of stay, or cost.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. This study demonstrated no improvement in pain scores at 30 minutes with the administration of IV ketamine. While they did demonstrate an increase in the need for IV morphine, the clinical significance of this outcome is very unclear. Additionally, this was a brief study looking only at 30-minute outcomes, and was conducted in a mobile ICU that does not exist in our practice.

Limitations:

1. **This was a relatively small study with only 65 patients. Potential clinically significant differences in key outcomes may have been discounted as statistically insignificant as a result (study power).**

2. **Outcomes were measured after a rather short time-period (30 minutes). Longer-term outcomes and ED length of study would be more helpful to assess for benefit or harm.**

3. **The study was conducted in France and enrolled patients being transported by a mobile ICU. These patients may have different comorbidities than ours, and no such EMS system exists in our community (external validity).**

Bottom Line:

In this methodologically sound, randomized, blinded, placebo-controlled trial, use of low-dose IV ketamine in addition to IV morphine in a mobile ICU reduced the need for further doses of morphine within 30 minutes with no improvement in patient satisfaction, but an increase in neuropsychological adverse events. Issues of external validity make it difficult to generalize these results to our patient population.