Critical Review Form
Therapy

Majidinejad S, Esmailian M, Emadi M. Comparison of Intravenous Ketamine with Morphine in Pain Relief of Long Bones Fractures: a Double Blind Randomized Clinical Trial. Emerg (Tehran). 2014 Spring;2(2):77-80.

Objectives: **"to evaluate the effect of ketamine alone on pain relief in trauma patients referring to an emergency unit of a third-level hospital." (p. 78)**

Methods: **This prospective, double blind, randomized controlled trial was conducted at two hospitals (Al-Zahra and Ayatollah Kashani Educational Centers) in Isfahan, Iran from 2012-2013. Consecutive adult patients, aged 18-55 years of age, presenting to the emergency unit with long bone fracture were eligible for enrollment. Patients with a history of drug abuse, head trauma, symptoms of elevated intracranial pressure, a decreased level of consciousness, a history of asthma, respiratory issues, history of cardiac disease, or contraindications to the administration of ketamine or morphine were excluded. Patients with a complication from the drug received in the study were also withdrawn and not included in the final analysis.**

Patients were randomly assigned to receive either IV morphine (0.1 mg/kg) or IV ketamine (0.5 mg/kg). Pain severity was assessed using the numeric rating scale (NRS) before injection and 10 minutes after injection of the study drug. Pain was considered to have subsided if there was a decrease in pain severity of 3 or more. In patients whose pain did not subside, a repeat injection was given at half the initial dose. A total of 126 patients were included in the study, 63 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. Patients were randomized in a 1:1 fashion to receive either IV morphine or IV ketamine.
2.	Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be	Uncertain. The method of randomization was not described. It is possible that the randomization scheme could have been subverted.

	"randomized" to a particular group?	
3.	Were patients analyzed in the groups to which they were randomized?	Uncertain. While the authors do not make mention of any crossover, and do not specifically mention using an intention to treat analysis, patients who suffered drug complications were excluded from the study. The authors do not tell us how many patients were withdrawn for this reason, but a true intention to treat analysis would not exclude such patients from the final analysis.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. Patients in the ketamine group were much younger than those in the morphine group (mean age 35.1±13.5 vs. 53.6±14,3), despite the reported lack of statistical significance ($p = 0.54$). There was also a higher rate of fractures in the lower extremities in the ketamine group compared to the morphine group (62.9% vs. 51.6%) though this did not achieve statistical significance ($p = 0.2$). Patients were similar with respect to baseline pain scores (8.8±0.8 vs. 8.9 ±0.8, $p = 0.32$).
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. "To make sure of the double-blind protocol of the study, preparation of the solutions, injections and registration of the results were carried out by three different physicians who had no contact or relationship with each other. The data on the injection of medications were available only to the chief researcher." (p. 78)
2.	Were clinicians aware of group allocation?	No. See above.
3.	Were outcome assessors aware of group allocation?	Yes. Outcomes were measured by patients, who were blinded to group allocation.
4.	Was follow-up complete?	Uncertain. The authors do not provide a flow chart of patients enrolled and analyzed. Patients with "a complication" from the drug administered were excluded from analysis. The authors do not define such complications, nor do they state how many patients were excluded on this basis.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• Pain severity decreased in both patients receiving IV ketamine (-2.7±1.8, $p < 0.001$) and IV morphine (-

		2.4±1.5, p < 0.001). There was no statistically significant difference in the amount by which pain was decreased in the two groups (p = 0.28). • Five minutes after injection, ketamine and morphine resulted in a successful decrease in pain severity in 33 (52.4%) patients and 38 (60.3%) patients, respectively; at 10 minutes after injection the number of patients with successful reduction in pain increased to 59 (93.7%) and 61 (96.8%), respectively. There was no significant difference in the number of patients with successful pain reduction between the groups (p = 0.62). • There were no complications observed in patients receiving morphine. Among patients receiving ketamine, 6 (9.5%) developed an emergence phenomenon, and 4 (6.3%) required a rescue dose.
2.	How precise was the estimate of the treatment effect?	The authors do not provide 95% confidence intervals, but these have been calculated where appropriate.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Somewhat. The authors of this study provided very little information regarding the patients enrolled. There is no information regarding medical comorbidities, the mechanism of injury, or the existence of additional injuries.. This study was performed in Iran, and it is likely that our patients would have more comorbidities.
2.	Were all clinically important outcomes considered?	No. The authors looked only at very short-term pain control and did not address long-term issues. They did not evaluate patient satisfaction, cost, or quality of life.
3.	Are the likely treatment benefits worth the potential harm and costs?	No. In this small study, IV morphine and IV ketamine had similar effects on pain scores, with significantly more patients receiving IV ketamine experiencing adverse effects. The results are limited by the small sample size and the short duration of follow-up (10 minutes).

Limitations:

1. **The authors failed to follow CONSORT guidelines for the reporting of a randomized trial, with a failure to provide the following:**

a. **There is no information regarding the method of randomization.**

b. **The method of blinding is poorly described and could easily be undermined.**

c. **A flow chart of patients enrolled, excluded, and analyzed.**

d. **Patient demographic information (i.e. medical comorbidities).**

e. **No 95% confidence intervals are provided.**

2. **Patients suffering "a complication" from the drug administered were excluded from the analysis. The authors do not define what constitutes "a complication," and they do not tell us how many patients were excluded on these grounds. Excluding such patients loses important information that would have been helpful if it were reported.**

3. **The primary outcome was measured 10 minutes after medication administration. Such short-term outcomes provide limited clinically relevant information.**

4. **The study did not address several important outcomes, such as patient satisfaction and ED length of stay.**

Bottom Line:

This small randomized, double blind trial demonstrated similar reductions in pain with injection of ketamine and morphine among patients with long bone fractures. A substantial proportion of patients in both groups had successful reduction in pain (93.7% in the ketamine group and 96.8% in the morphine group). This study is very limited by lack of proper reporting according to Consort guidelines, as well as the use of short-term outcomes and a very high dose of ketamine (0.5 mg/kg).