Critical Review Form
Case Series

Olives TD, Nystrom PC, Cole JB, Dodd KW, Ho JD. Intubation of Profoundly Agitated Patients Treated with Prehospital Ketamine. Prehosp Disaster Med. 2016 Sep 19:1-10.

Objectives: **"to define the rate of intubation in profoundly agitated patients receiving prehospital ketamine at high (>5mg/kg) and low (≤5mg/kg) doses, and to describe clinically important outcomes associated with this therapy." (p. 2)**

Methods: **This retrospective cohort study was conducted using records from Hennepin County Medical Center in Minneapolis, Minnesota and its associated EMS system. Adults patients (age 18 years or older) receiving prehospital ketamine for control of profound agitation between May 1, 2010 and August 31, 2013 were eligible for inclusions. Cases were identified by searching the prehospital service database. Patients who were pregnant, who received ketamine for analgesic properties, or who were transported to other facilities were excluded from the study. Per protocol, ketamine was administered as an intramuscular (IM) injection at a dose of 5 mg/kg; in the rare case where IV access was already established, up to 2 mg/kg could be administered intravenously.**

Two authors abstracted data from the electronic medical record and entered such data electronically into a data collection sheet. The records were reviewed for evidence of clinically significant adverse events related to ketamine administration, including intubation and the indication for intubation.

Prehospital ketamine was administered on 227 occasions, of which 92 were excluded. There were 135 episodes of prehospital ketamine administration for profound agitation. Of these, 80% were male, 60 (44%) had a heart rate of 120 or greater on presentation, and 48 (35%) had a systolic blood pressure > 160 mm Hg. There 85 patients who required intubation (63%), 4 of whom (2.96%) were intubated by EMS in the field. The median age among intubated patients was 31 and the median age among non-intubated patients was 32. Intubated patients were more likely to be male (89.4% vs. 64.0%), but had similar initial vital signs to those who were not intubated and received similar doses of ketamine (median 5.25 mg/kg and 5.14 mg/kg).

Guide		Comments
A.	**Are the results valid?**	
1.	Were there clear criteria for inclusion in the case series?	Yes. Only adult patients requiring prehospital administration of IM ketamine, specifically for profound agitation, were eligible for inclusion.
2.	Was the condition identified and measured in a standard, reliable way for all participants included?	No. The condition (profound agitation) was highly subjective, determined at the time of the encounter by the treating paramedics. It is possible that some patients may have suffered from medical conditions (i.e. delirium, dementia) that would preclude the use of ketamine.
4.	Were consecutive patients included and was inclusion complete?	Yes and no. Purportedly, all patients who received IM ketamine under the treating agencies' protocols for profound agitation during the specified time period were included in the analysis. However, the authors do not make it clear if some agitated patients were treated with alternate regimens (i.e. haloperidol or midazolam), and if such patients differed in some appreciable way from the included patients.
5	Was sufficient demographic information provided for included patients?	No. The authors provide detailed information regarding initial vital signs, age, gender, and time of presentation, but fail to provide much information regarding medical and psychiatric history, and provide no information regarding the perceived cause of the patients' agitation.
6.	Was follow-up of subjects long enough to detect the outcome of interest?	Yes. The outcome of interest was the need for intubation, which should be apparent by EMS and ED records alone.
7.	Was follow-up complete?	Yes. There appears to be outcome data for all 135 patients included in the study.
B.	**What were the results?**	
1.	What were the outcomes?	There were 85 patients who required intubation (63%, 95% CI 55% to 71%), 4 of whom (3%, 95% CI 1% to 7%) were intubated by EMS in the field. • The median age among intubated patients was 31 and the median age among non-intubated patients was 32. • Intubated patients were more likely to be male (89.4% vs. 64.0%, p = 0.001). • Intubated vs. nonintubated patient received similar doses of ketamine (median 5.25 mg/kg and 5.14 mg/kg), and need for intubation was not associated with the administration of high-dose (>5 mg/kg) vs. low-dose (≤ 5 mg/kg) ketamine. • Need for intubation was statistically

		associated with male gender (p = 0.001) and arrival during an overnight shift (p = 0.021). • Using logistic regression modeling for 120 subjects with adequate data available, the association between male gender and intubation persisted (adjusted odds ratio 1.91, 95% CI 1.14 to 3.21), as did late night arrival (OR 2.57, 95% CI 1.05 to 6.27). Age, ketamine dosing, and co-administration of haloperidol or midazolam were NOT associated with intubation in this model.
2.	How precise was the estimate of the outcomes? (i.e. what were the 95% confidence intervals?)	See above.
C.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	No. Not even close. The fact that nearly two thirds of patients receiving IM ketamine for agitation ended up requiring intubation suggests that either the population itself was very different from those seen in our practice setting, or that practice pattern at this institution is completely different from our own. Either way, it will be very difficult to interpret the results of this study in such a way that we can apply the results to our patient population and setting in any meaningful way (external validity).
2.	Were all clinically important outcomes considered?	No. The authors did not evaluate ED length of stay, hospital length of stay, cost, or explore the possible reasons that such a large percent of patients required intubation.
3.	What are the implications of the results? Are the likely treatment benefits worth the potential harm and costs?	This data suggests that use of ketamine for profound agitation leads to an extremely large intubation rate (63%). As the authors do not compare this cohort to a similar cohort receiving alternative sedative agents (i.e. haloperidol) and do not report historic intubation rates, it is unclear if this high intubation is a reflection is due to the use of ketamine, or a reflection of a different practice pattern.

Limitations:

1. **Inclusion in the study required that the patient have "profound agitation," which is very subjective and likely influenced by the bias of the prehospital personnel.**

2. **The study notes a very high intubation rate (63%) among patients requiring IM ketamine for profound agitation. This rate is much higher than that reported in other trials: 23% reported by Keseg et al, 4% reported by Scheppke et al.**

3. **This study does not address important "long-term" clinical outcomes, such as ED length of stay, hospital length of stay, need for ICU admission, or cost.**

4. **This study was comprised of a single arm, and hence does not allow comparison of treatment efficacy or adverse events to traditional methods of chemical restraint.**

Bottom Line:

This retrospective cohort study identified 135 episodes of ketamine administration for profound agitation in the prehospital setting. Among these patients, intubation rates were exceedingly high (63%, 95% CI 55% to 71%), and after logistic regression to control for confounding factors, was associated with male gender and night-time presentation. These high rates are very out of line with previous studies, suggesting a possible difference in practice pattern at the receiving facility.