Critical Review Form
Therapy

PGY-2

Cole JB, Moore JC, Nystrom PC, Orozco BS, Stellpflug SJ, Kornas RL, Fryza BJ, Steinberg LW, O'Brien-Lambert A, Bache-Wiig P, Engebretsen KM, Ho JD. A prospective study of ketamine versus haloperidol for severe prehospital agitation. Clin Toxicol (Phila). 2016 Aug;54(7):556-62.

Objectives: **"to determine if haloperidol or ketamine was superior for the treatment of severe prehospital acute undifferentiated agitation." (p. 556)**

Methods: **This prospective observational study enrolled patients with severe acute, undifferentiated agitation being transported by EMS to the Hennepin County Medical Center ED in Minneapolis, MN between October 2014 and September 2015. Adult patients aged 18 years or older with an Altered Mental Status Scale (AMSS) score of +2 or +3 determined by the paramedics were eligible for inclusion, regardless of the suspected etiology. Women who were obviously gravid, subjects who were known to be or appeared to be younger than 18 years of age, and those with "profound agitation" (defined as an AMSS score of +4) were excluded.**

For the first three months of the study (October-December 2014), EMS protocol dictated that patients with undifferentiated agitation were treated with haloperidol (10 mg IM). From January-June 2015, haloperidol was removed from all ambulances, and protocol dictated treatment with ketamine (5 mg/kg IM). From July-September 2015, haloperidol was once again reinstated in all ambulances and became the standard treatment for agitation. All paramedics were trained in the AMSS score (online and by in-person training) and were required to pass a quiz.

The primary outcome was time to adequate sedation, measured by a stopwatch that was activated by EMS personnel immediately after sedative injection. AMSS scores were then recorded every 5 minutes, and while adequate sedation was defined clinically by the treating paramedic, it was emphasized that an AMSS score of +1 should be considered adequate. In cases where adequate sedation did not occur prior to arrival in the ED, AMSS scores were recorded every 5 minutes in the ED by a research assistant. Secondary outcomes included need for redosing of medications in the prehospital setting, rates of adverse medication effects, and rates of intubation.

A total of 343 patients with an AMSS score of +2 or +3 were encountered by EMS. Of these, 143 were excluded because a trained research assistant or medic was not available, 48 were transported to another facility, and 6 had incomplete data. This left 146 patients enrolled: 64 received ketamine and 82 received haloperidol. For the entire cohort, median scene time was 22 minutes and median transport time was 8 minutes. The median dose in the ketamine group was 5.2 mg/kg IM (range 1.7-8.5); all patients in the haloperidol group received 10 mg/kg IM except for 5 who received 5 mg IM.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis?**	
1.	Were patients randomized?	No. This was an observational trial and was not randomized, and hence was subject to selection bias. Patients received ketamine or haloperidol based on EMS protocol at that time, which varied over the course of the year so that haloperidol was given for 6 months and ketamine for 6 months.
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?	N/A
3.	Were patients analyzed in the groups to which they were randomized?	N/A. The authors specifically note that "subjects were analyzed as intention to treat," though there does not appear to be any crossover between the groups, and treatment group was determined by the time of year in which they received treatment.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Somewhat. Patients were similar with respect to age, gender, and history of mental illness. Patients in the ketamine group were somewhat more agitated than those in the haloperidol group (89% with an AMSS score of 3+ in the ketamine group vs. 73% in the haloperidol group) and had somewhat higher initial heart rates and systolic blood pressures. Patients in the haloperidol group were more likely to have history of chemical dependency (72% vs. 47%).
B.	**Did experimental and control groups retain a similar prognosis after the study started?**	
1.	Were patients aware of group allocation?	No. While patients were not blinded, it is unlikely that they were routinely made aware of what medication they were being given. Given their state of agitation, it is unlikely that performance bias on the part of the patient would have affected outcomes.
2.	Were clinicians aware of group allocation?	Yes. This was not a blinded study, and both EMS personnel and ED physicians were aware of the study medication being given. It is possible, given the nature of the study, that some degree of performance

		bias on the part of the clinicians could have influenced practice and affected outcomes.
3.	Were outcome assessors aware of group allocation?	Yes. Again, this was not a blinded study. EMS personnel and research assistants, who determined when the primary outcome (adequate sedation) had been reached, could have been influenced by their knowledge of the drug being administered. It is possible that observer bias could have affected outcomes.
4.	Was follow-up complete?	Yes. Outcome data was available for all patients.
II.	**What are the results ?**	
1.	How large was the treatment effect?	• Time to adequate sedation was significantly faster among patients receiving ketamine compared to those receiving haloperidol: median 5 minutes vs. 17 minutes, absolute difference (AD) 12 minutes (95% CI 9-15). • Adequate sedation was achieved in the prehospital setting more often in the ketamine group vs. the haloperidol group: 95% vs. 65%, AD 30% (95% CI 18% to 42%). • Additional sedation medication was required more often in the haloperidol group compared to the ketamine group: 20% vs. 5%. • The complication rate was significantly higher in the ketamine group compared to the haloperidol group: 49% vs. 5%, AD 44% (95% CI 30% to 57%). • Intubation was significantly more common in the ketamine group compared to the haloperidol group: 39% vs. 4%, AD 35% (95% CI 23% to 48%) for a number needed to harm (NNH) of 2.9. • Patients receiving haloperidol were significantly more likely to go home from the ED (52% vs. 19%), while those receiving ketamine were more likely to be hospitalized or admitted to the ICU (44% vs. 6%).
2.	How precise was the estimate of the treatment effect?	See above.
III.	**How can I apply the results to patient care?**	
1.	Were the study patients similar to my patient?	Likely yes. These were acutely agitated patients being cared for by EMS in a large US city who were transported to an urban level 1 trauma center. A large percentage of patients had a history of mental illness

		and a history of chemical dependency, which seems in keeping with agitated patients cared for in our system. While the racial profile of these patients is likely different from those in our institution (higher proportion of Caucasian and American Indian individuals, lower proportion of African Americans) it seems unlikely that this would affect outcomes in any meaningful way.
2.	Were all clinically important outcomes considered?	No. The authors considered most important short-term outcomes, but did not address ED or hospital length of stay, cost, or patient/family satisfaction. Uncertain. This study suggests that use of ketamine results in more rapid and reliable sedation of acutely agitated patients, with an associated increased risk of adverse effects, including need for intubation (with a NNT of around 3). While rapid and reliable sedation of agitated patients is important, and should decrease the risks that both patients and healthcare providers face in such situations (e.g. rhabdomyolysis, cardiac dysrhythmias, self-harm, assault) it is unclear if this decreased risk is worth the significant increase harm associated with ketamine administration.
3.	Are the likely treatment benefits worth the potential harm and costs?	No. While time to sedation was much faster for patients receiving ketamine, this was accompanied by a much higher incidence of intubation and ICU admission. The potential risks of intubation and increased cost associated with admission to the ICU far outweigh the 12-minute improvement in median time to sedation.

Limitations:

1. **This was a nonrandomized study with high potential for selection bias.**
2. **The two groups were not well balanced, with those in the ketamine group having higher agitations scores, higher heart rates, and higher blood pressures. Patients in the haloperidol group were more likely to have a history of chemical dependence.**
3. **Lack of blinding in this study may have resulted in both performance bias and observer bias.**
4. **Despite EMS protocol stipulating a ketamine dose of 5 mg/kg, the actual dosages varied widely, with a range of 1.7 to 8.5 mg/kg. This deviation from protocol may have resulted in the high intubation rates seen.**

Bottom Line:

This prospective observational study of IM ketamine vs. haloperidol for management of agitation in the prehospital setting demonstrated decreased time to sedation with the use of ketamine (median 5 vs. 17 minutes) with a significant increase in the need for intubation (39% vs. 4%) and rates of ICU admission (44% vs. 6%). Based on these results, it seems that the benefits of ketamine administration are far outweighed by the risks.