

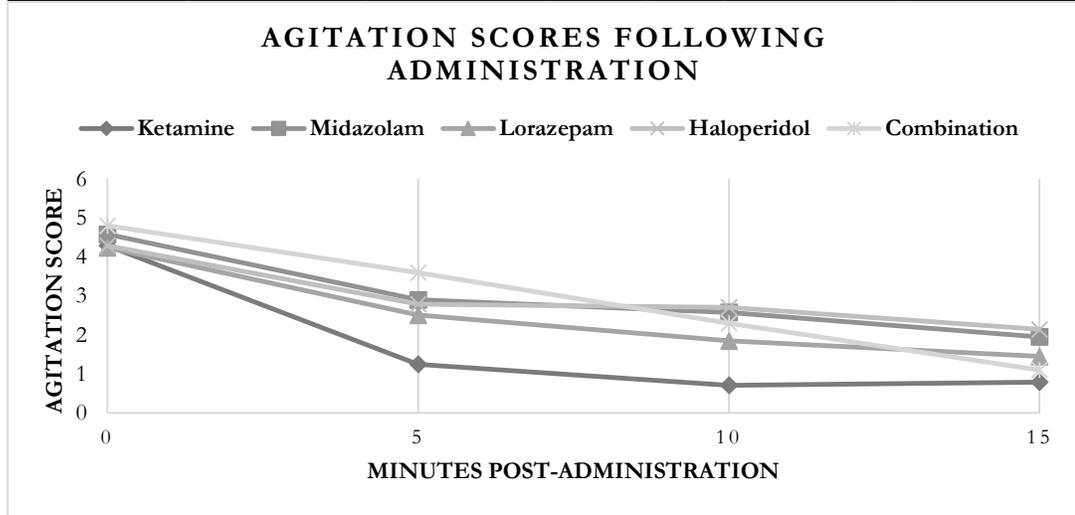
**Ketamine as a first-line treatment for severely agitated emergency department patients.**

Am J Emerg Med 2017;35:1000-1004.

<b>Background and Overview</b>	
<b>Background</b>	<ul style="list-style-type: none"> <li>• Acutely agitated patients are frequently seen in the emergency department (ED), and may pose a danger to themselves and those around them, including ED staff.</li> <li>• Commonly used medications to manage acute agitation include benzodiazepines (primarily midazolam and lorazepam) and antipsychotics (both typical and atypical)               <ul style="list-style-type: none"> <li>○ These options are generally limited by slow onset, respiratory depression, and variability in clinical response</li> </ul> </li> <li>• Recently, ketamine has begun to be considered as an alternative to the above agents for this indication.               <ul style="list-style-type: none"> <li>○ Ketamine's rapid onset and hemodynamic stability may allow it to avoid some of the limitations of other options</li> <li>○ Previous studies have examined ketamine use for this indication in the pre-hospital setting (Cole et al, 2016) and as a third-line option when traditional therapy fails (Isbister et al., 2016).</li> <li>○ There is a current paucity of literature regarding ketamine use as a first-line agent.</li> </ul> </li> </ul>
<b>Objective</b>	To compare the time to a defined reduction in agitation scores for ketamine versus benzodiazepines and haloperidol alone or in combination
<b>Methods</b>	
<b>Study Design</b>	Single-center, prospective, observational study
<b>Funding</b>	The University of California, San Francisco Clinical & Translocational Science Institute
<b>Inclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Adults (18-65) requiring chemical sedation for acute agitation according to an ED resident or attending who are triaged to a high acuity area with cardiorespiratory monitoring</li> </ul>
<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Pregnant women</li> <li>• Prisoners / persons in police custody</li> <li>• Triaged to low-acuity zone without appropriate monitoring</li> </ul>
<b>Interventions</b>	<ul style="list-style-type: none"> <li>• Dosages based on current practice guidelines</li> <li>• Ketamine: 4-6 mg/kg IM or 1-2 mg/kg IV</li> <li>• Haloperidol: 5-10 mg IM</li> <li>• Midazolam: 5-10 mg IM or 5 mg IV</li> <li>• Lorazepam: 1-2 mg IM or IV</li> <li>• Combination lorazepam and haloperidol</li> </ul>
<b>Outcome Measures</b>	<ul style="list-style-type: none"> <li>• Primary endpoint               <ul style="list-style-type: none"> <li>○ Reduction in agitation scores for ketamine versus comparators, based on a previously-validated 6-point scale                   <ul style="list-style-type: none"> <li>▪ Recorded by physician 4 times per patient                       <ul style="list-style-type: none"> <li>• Prior to medication administration (0 minutes), and 5, 10, and 15 minutes post-administration</li> </ul> </li> <li>▪ Also documented time at which adequate sedation achieved</li> <li>▪ Adequate sedation defined as <math>\leq 2</math></li> </ul> </li> </ul> </li> <li>• Secondary endpoints (abstracted from health records retrospectively)               <ul style="list-style-type: none"> <li>○ Repeat medication dosing</li> <li>○ Changes in vital signs / incidence of adverse events</li> </ul> </li> </ul>
<b>Statistical Analysis</b>	<ul style="list-style-type: none"> <li>• Continuous data and percentages: mean, median, and standard deviation</li> <li>• Categorical data: chi-squared statistics (bivariate) and ANOVA (univariate)</li> <li>• Data adjusted for multiple comparisons</li> <li>• Two-sided <math>p &lt; 0.05</math> criterion for statistical significance</li> </ul>
<b>Results</b>	
<b>Baseline Characteristics</b>	<ul style="list-style-type: none"> <li>• Total participants enrolled: n = 106               <ul style="list-style-type: none"> <li>○ Total eligible: n = 98 (8 excluded)</li> </ul> </li> <li>• All groups primarily male</li> <li>• Ketamine group: ~10 years younger than all other groups</li> </ul>

**Efficacy Endpoints**

Agitation Scoring (Richards et al., 1998)					
6	5	4	3	2	1
Combative, violent, out of control	Very anxious, agitated, loud outbursts	Anxious, restless, in control	Awake, cooperative, tranquil	Somnolent, easily arousable	Deep sleep



- Secondary Outcomes
  - Need for repeat dosing: no significant difference between groups
  - Not powered for secondary outcomes

**Safety Endpoints**

- No significant differences between ketamine and comparators in changes in PR, SBP, or need for intubation (inadequately powered for safety endpoints)

**Conclusions and Discussion**

**Discussion**

- Ketamine provided superior control of agitation at all study time points, but is unlikely to resolve any underlying cause of agitation
- Author’s limitations
  - Study population exhibited higher-than-usual methamphetamine abuse
  - Selection bias possible due to lack of randomization
  - Physicians blinded to hypothesis, but not medications
  - Dosing was not uniform and varied among medications
  - Vital sign data limited to 1-hour post-administration
  - Did not account for pre-hospital treatment
- Evaluator’s limitations
  - Random assignment to treatment groups does not optimize therapy
  - The study’s definition of appropriate sedation may have over-sedated patients and biased the results to favor ketamine
    - If sedation is the primary goal of therapy, other medications may warrant consideration as well
  - Author’s may have unnecessarily excluded patients based on acuity
- Conclusion: Ketamine appears to be faster at controlling agitation than standard ED medications and can be considered as effective as a first-line sedating agent.

**Application**

- Currently at the MCH ED, sedation due to acute agitation is required nearly every day.
  - All discussed treatments above (including ketamine) are utilized when deemed necessary
  - The findings in this study strengthen the rationale supporting current practice
- Patients in whom ketamine would be inappropriate:
  - Head trauma
  - Known or suspected psychiatric illness
  - Known or suspected cardiovascular disease
- Patients in whom ketamine would be appropriate:
  - Low pre-treatment SBP/PR
  - Other agents contraindicated or otherwise inappropriate

**References**

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