### Background

- 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.
- Commonly used medications to manage acute agitation include benzodiazepines (primarily midazolam and lorazepam) and antipsychotics (both typical and atypical)
  - These options are generally limited by slow onset, respiratory depression, and variability in clinical response
- Recently, ketamine has begun to be considered as an alternative to the above agents for this indication.
  - Ketamine’s rapid onset and hemodynamic stability may allow it to avoid some of the limitations of other options
  - 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 (Ibister et al., 2016).
  - There is a current paucity of literature regarding ketamine use as a first-line agent.

### Objective

To compare the time to a defined reduction in agitation scores for ketamine versus benzodiazepines and haloperidol alone or in combination.

### Methods

#### Study Design

Single-center, prospective, observational study

#### Funding

The University of California, San Francisco Clinical & Translational Science Institute

#### Inclusion Criteria

- 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

#### Exclusion Criteria

- Pregnant women
- Prisoners / persons in police custody
- Triaged to low-acuity zone without appropriate monitoring

#### Interventions

- Dosages based on current practice guidelines
- Ketamine: 4-6 mg/kg IM or 1-2 mg/kg IV
- Haloperidol: 5-10 mg IM
- Midazolam: 5-10 mg IM or 5 mg IV
- Lorazepam: 1-2 mg IM or IV
- Combination lorazepam and haloperidol

#### Outcome Measures

- Primary endpoint
  - Reduction in agitation scores for ketamine versus comparators, based on a previously-validated 6-point scale
    - Recorded by physician 4 times per patient
    - Prior to medication administration (0 minutes), and 5, 10, and 15 minutes post-administration
    - Also documented time at which adequate sedation achieved
    - Adequate sedation defined as ≤2
  - Secondary endpoints (abstracted from health records retrospectively)
    - Repeat medication dosing
    - Changes in vital signs / incidence of adverse events

#### Statistical Analysis

- Continuous data and percentages: mean, median, and standard deviation
- Categorical data: chi-squared statistics (bivariate) and ANOVA (univariate)
- Data adjusted for multiple comparisons
- Two-sided $p < 0.05$ criterion for statistical significance

### Results

#### Baseline Characteristics

- Total participants enrolled: n = 106
  - Total eligible: n = 98 (8 excluded)
- All groups primarily male
- Ketamine group: ~10 years younger than all other groups
Efficacy Endpoints

<table>
<thead>
<tr>
<th>6</th>
<th>5</th>
<th>4</th>
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<tbody>
<tr>
<td>Combative, violent, out of control</td>
<td>Very anxious, agitated, loud outbursts</td>
<td>Anxious, restless, in control</td>
<td>Awake, cooperative, tranquil</td>
<td>Somnolent, easily arousable</td>
<td>Deep sleep</td>
</tr>
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**Agitation Scoring**

(Richards et al., 1998)

**AGITATION SCORES FOLLOWING ADMINISTRATION**

- 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


Special thanks to Jan Ramos, Pharm.D., who shared his knowledge of current practice with regard to this topic in the MCH ED.