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Original Contribution

# Ketamine as a first-line treatment for severely agitated emergency department patients☆

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ABSTRACT

*Objective:* Emergency physicians often need to control agitated patients who present a danger to themselves and hospital personnel. Commonly used medications have limitations. Our primary objective was to compare the time to a defined reduction in agitation scores for ketamine versus benzodiazepines and haloperidol, alone or in combination. Our secondary objectives were to compare rates of medication redosing, vital sign changes, and adverse events in the different treatment groups.
*Methods:* We conducted a single-center, prospective, observational study examining agitation levels in acutely agitated emergency department patients between the ages of 18 and 65 who required sedation medication for acute agitation. Providers measured agitation levels on a previously validated 6-point sedation scale at 0-, 5-, 10-, and 15-min after receiving sedation. We also assessed the incidence of adverse events, repeat or rescue medication dosing, and changes in vital signs.
*Results:* 106 patients were enrolled and 98 met eligibility criteria. There was no significant difference between groups in initial agitation scores. Based on agitation scores, more patients in the ketamine group were no longer agitated than the other medication groups at 5-, 10-, and 15-min after receiving medication. Patients receiving ketamine had similar rates of redosing, changes in vital signs, and adverse events to the other groups.
*Conclusion:* In highly agitated and violent emergency department patients, significantly fewer patients receiving ketamine as a first line sedating agent were agitated at 5-, 10-, and 15-min. Ketamine appears to be faster at controlling agitation than standard emergency department medications.



## 1. Introduction

### 1.1. Background

Emergency physicians often need to control violent, psychotic, or intoxicated patients who present a danger to themselves and hospital personnel. Rational reasoning, bargaining, shows of force with security guards, and even physical restraint are sometimes ineffective in controlling the acutely agitated patient. Chemical sedation is sometimes necessary to prevent injuries to patients and staff, and to allow safe medical evaluation and treatment. Benzodiazepines and typical antipsychotics such as haloperidol, the most commonly used sedative agents, have limitations including slow onset, respiratory depression, and variability in clinical response [1,2].

### 1.2. Importance

While several recent studies have shown the efficacy of ketamine for sedation in the prehospital setting [3,4] and as a rescue medication in emergency department (ED) patients who failed previous sedation attempts [5], there is limited data evaluating the effectiveness of ketamine as a first line agent for sedating agitated patients in the ED.

### 1.3. Goals of this investigation

The goal of our study was to compare the effectiveness and safety of ketamine to standard sedatives in agitated ED patients. Specifically, our primary objective was to compare the time to a defined reduction in agitation scores for ketamine versus benzodiazepines and haloperidol, alone or in combination. Our secondary objective was to assess the incidence of adverse events, repeat or rescue medication dosing, and changes in vital signs. We hypothesized that ketamine would produce the desired clinical effect in a shorter time, with similar side effects, stable hemodynamics, and less repeat dosing.

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**Table 1**
Study group demographics.

| | Ketamine (n = 24) | Midazolam (n = 17) | Lorazepam (n = 33) | Haloperidol (n = 14) | Combo (n = 10) | p |
|---|---|---|---|---|---|---|
| Median age (range) | 29 (19–58) | 43 (18–51) | 43 (20–63) | 44 (21–58) | 40.5 (21–58) | 0.033 |
| Male sex, no. (%) | 19 (79.2%) | 18 (94.7%) | 19 (57.6%) | 11 (78.6%) | 9 (90.0%) | 0.026 |
| Race, no. (%) | | | | | | |
| African American | 3 (12.5%) | 1 (5.3%) | 5 (15.2%) | 1 (7.1%) | 1 (10.0%) | 0.931 |
| Asian | 1 (4.3%) | 0 (0.0%) | 1 (3.1%) | 1 (7.1%) | 0 (0.0%) | |
| Hispanic | 10 (41.7%) | 10 (52.6%) | 13 (39.4%) | 8 (57.1%) | 7 (70.0%) | |
| White | 10 (43.5%) | 7 (36.8%) | 13 (40.6%) | 4 (28.6%) | 2 (20.0%) | |
| Drug use, no. (%) | | | | | | |
| Yes | 13 (54.2%) | 12 (63.2%) | 26 (78.8%) | 12 (85.7%) | 6 (60.0%) | 0.168 |
| No | 11 (47.8%) | 7 (36.8%) | 7 (21.9%) | 2 (14.3%) | 4 (40.0%) | |
| Unknown | | | | | | |
| Alcohol use, no. (%) | | | | | | |
| Yes | 8 (33.3%) | 8 (42.1%) | 8 (24.2%) | 5 (35.7%) | 2 (20.0%) | 0.365 |
| No | 12 (52.2%) | 7 (36.8%) | 14 (21.9%) | 5 (35.7%) | 2 (20.0%) | |
| Unknown | 4 (17.4%) | 4 (21.1%) | 11 (34.4%) | 4 (28.6%) | 6 (60.0%) | |
| Prior psychiatric visits, no. (%) | | | | | | |
| Yes | 7 (30.4%) | 7 (36.8%) | 17 (53.1%) | 7 (50.0%) | 5 (50.0%) | 0.459 |

## 2. Methods

### 2.1. Study design

This was a single-center, prospective, observational study examining agitated ED patients requiring medication for sedation. IRB approval was obtained from our local institution.

### 2.2. Setting and participants

The study took place at a single urban level one trauma center ED with an annual census of 115,000 visits. A convenience sample was enrolled from May 2013 to January 2015.

Acutely agitated patients between the ages of 18 and 65 who required chemical sedation for acute agitation according to an emergency medicine resident or attending physician were eligible for enrollment. Pregnant women, prisoners and persons in police custody were excluded. Also excluded were those triaged to a low acuity zone of the ED that did not have continuous cardiorespiratory monitoring. Our study population included only those patients so severely agitated that they required care in a high acuity treatment area with available cardiorespiratory monitoring.

### 2.3. Variables

We initially defined four groups for comparison: ketamine, benzodiazepines, haloperidol, and a benzodiazepine plus haloperidol. Because the benzodiazepine group was comprised entirely of midazolam and lorazepam, we considered them separately, and compared a total of five groups. Due to the observational nature of this study, medication dosages were not uniform. Current published dosage recommendations for these medications include: ketamine 4–6 mg/kg intramuscular (IM) or 1–2 mg/kg intravenous (IV) [6-7], haloperidol 5–10 mg IM [8], midazolam 5–10 mg IM [9] or 5 mg IV[10], lorazepam 1–2 mg IV or IM [11].

### 2.4. Outcomes

Providers measured the patients' agitation on a previously validated 6-point sedation scale that was developed to monitor changes in agitation in ED patients [10,12]. In keeping with previous studies, adequate sedation was defined as an agitation score of ≤2 (see Appendix). Agitation was recorded by the treating physician prior to medication administration and at 5-, 10-, and 15-min after medication administration. Providers also recorded the time at which they thought adequate sedation had been achieved.

The incidence of adverse events, repeat or rescue medication dosing, and changes in vital signs were retrospectively abstracted from the electronic health record.

### 2.5. Measurement

ED physicians completed a structured data collection form (see Appendix). One trained author (AT) reviewed the relevant portion of each patient's medical record for the index visit and any return visits to our ED within 7 days. The abstractor was blinded to the study hypothesis until abstraction was complete. The abstractor received two 90-

**Table 2**
Study group dispositions.

| | Ketamine | Midazolam | Lorazepam | Haloperidol | Combo | p |
|---|---|---|---|---|---|---|
| Disposition, no. (%) | | | | | | |
| Hospital admission | 14 (58.3%) | 10 (52.6%) | 15 (46.9%) | 7 (50.0%) | 3 (30.0%) | 0.944 |
| Psychiatric admission | 8 (33.3%) | 1 (5.3%) | 2 (6.3%) | 1 (7.1%) | 1 (10.0%) | |
| Discharge home | 2 (8.3%) | 8 (42.1%) | 15 (46.9%) | 6 (42.9%) | 6 (60.0%) | |
| Admission location, no. (%) | | | | | | |
| Intensive care unit | 7 (29.2%) | 5 (26.3%) | 2 (6.3%) | 3 (21.4%) | 1 (10.0%) | 0.412 |
| Stepdown unit | 1 (4.2%) | 3 (15.8%) | 4 (12.5%) | 2 (14.3%) | 0 (0.0%) | |
| Telemetry floor | 1 (4.2%) | 0 (0.0%) | 3 (9.4%) | 1 (7.1%) | 0 (0.0%) | |
| Unmonitored floor | 5 (20.8%) | 2 (10.5%) | 6 (18.8%) | 1 (7.1%) | 1 (10.0%) | |
| LOS ED, minutes (SD) | 332.7 (242.8) | 402.5 (304.9) | 356.2 (298.4) | 301.1 (193.3) | 388.6(394.4) | 0.865 |
| LOS ICU, hours (SD) | 157.8 (131.3) | 182.0 (91.2) | 123.0 (−) | 236 (137.2) | 0.0 | 0.889 |
| LOS Hosp[a] | 105.6 (97.7) | 140.3 (99.4) | 96.5 (106.7) | 110.8 (99.0) | 95.0 (44.6) | 0.899 |
| 48 h bounceback[b] | 2 (8.3%) | 2 (10.5%) | 2 (6.1%) | 1 (7.1%) | 0 (0.0%) | 0.062 |

[a] Hospital length of stay only if admitted.
[b] Return ED visit within 48 h only if discharged home from the ED.

**Table 3**
Doses of medications administered during study.

| | n | Mean dose (Mg)[a] | | | Range | | |
|---|---|---|---|---|---|---|---|
| | | IV | IM | IN | IV | IM | IN |
| Ketamine (Mg/kg) | 24 | 0.87 (n = 18) | 2.97 (n = 6) | – | 0.31–2.20 | 0.88–3.94 | – |
| Midazolam (mg) | 19 | 3.08 (n = 12) | 2.25 (n = 4) | 2.00 (n = 3) | 1.00–4.00 | 1.00–4.00 | 2.00 |
| Lorazepam (mg) | 33 | 1.90 (n = 28) | 2.40 (n = 5) | – | 1.00–4.00 | 2.00–4.00 | – |
| Haloperidol (mg) | 14 | – | 5.71 (n = 14) | – | – | 5.00–10.00 | – |
| Combo (mg) | 10 | L: 2.00 (n = 5) | H: 5.00 (n = 10)<br>L: 2.00 (n = 5) | – | L: 2.00 | H: 5.00<br>L: 2.00 | – |

[a] L = lorazepam, H = haloperidol, IM = intramuscular. IV = intravenous. – = medication not given.

minute training sessions. A written definition of each variable guided the data abstraction (see Appendix). Early in the course of abstraction, a second author (JR) independently abstracted a random sample of 5 charts. Out of a possible 235 data points, there were 3 items of disagreement (1.3%). None of the discrepancies were related to the primary or secondary outcomes involving medication, doses, sedation scores, or adverse events.

### 2.6. Sample size

In order to calculate our necessary sample size, we assumed that 5 min was the smallest difference in time to sedation that would be clinically significant. Based on an expected mean time to sedation in the standard sedation groups of 15 min, with an estimated standard deviation of 5 min, 80% power, and alpha of 0.05, we determined that 17 participants were needed in each group.

### 2.7. Analysis

All data was entered into an Excel spreadsheet (Microsoft, Redmond, WA) where basic descriptive statistics were performed. Means, medians and standard deviations were computed for continuous variables and percentages for categorical data. Bivariate analyses of categorical variables by treatment were conducted using chi-squared statistics. Univariate analysis of variance was used for comparing continuous variables by treatment. All analyses between medications were adjusted for multiple comparisons. Analyses were performed in Stata v. 14.2 (College Station, TX) and two-sided $p < 0.05$ was used as the criterion for statistical significance.

## 3. Results

During the study period, 106 patients were enrolled and 98 met eligibility criteria. Demographic data is presented in Table 1, with groups based on initial medication given. Those receiving ketamine were significantly younger than those receiving other medications ($p = 0.033$) and the entire study cohort was mostly male. There were no significant differences based on race, stated use of substances, or previous psychiatric history. There were no significant differences in disposition based on study group (Table 2).

Mean doses of medications administered are presented in Table 3.

There was no significant difference between groups in initial agitation scores (Table 4). Most patients were “highly aroused” or “violent” prior to receiving medication. Based on agitation scores at 5-, 10-, and 15-min after receiving medication, more patients in the ketamine group were no longer agitated than the other medication groups ($p = 0.001$, $p \leq 0.001$, $p = 0.032$). There was no significant difference between groups in provider's reported time until agitation was subjectively controlled.

There was no significant difference between groups in the requirement for subsequent redosing of sedative medication (Table 5).

There was a significant difference in the pulse rate reduction within the first hour seen with midazolam (Table 6). No other significant differences in pulse rate or blood pressure were found. The single greatest increase in SBP in a patient given ketamine was 75 mm Hg. The patient received naloxone just prior to ED arrival from EMS.

Two patients receiving ketamine were intubated. One patient each receiving midazolam, lorazepam, haloperidol, and combo haloperidol plus benzodiazepine were intubated (Appendix).

## 4. Discussion

In this prospective evaluation of ketamine as a first line agent for sedation of agitation emergency department patients, we found that significantly more patients receiving ketamine had their agitation controlled at all study time points. Though not powered to detect secondary outcome differences, patients receiving ketamine had similar rates of redosing, changes in vital signs, and adverse events.

A vast body of literature exists supporting the use of ketamine for procedural sedation and intubation [13-16]. While the literature on its use in agitated patients is less robust, ketamine has been used to control agitation in prehospital, aeromedical, military, and ED settings [3,4,17-22].

The only study that has evaluated the effectiveness of ketamine sedation for agitation in the ED comes from a subgroup analysis of patients who received droperidol or midazolam and then had intramuscular ketamine added after the other medications were ineffective [5]. The mean time to sedation post-ketamine was 20 min, and they concluded ketamine appears to be a reasonable 3rd line agent for sedation of patients with acute behavioral disturbance. Our study adds to this by suggesting that ketamine is effective as a first-line sedating agent. Our mean time to control of sedation was much faster. This may be explained by the high number in our cohort receiving the medication intravenously (18/24, 75%), though our time was consistent with a prehospital study that found a mean time to sedation post-intramuscular ketamine of 5.5 min [4].

A recent retrospective study evaluating adverse events in 27 agitated patients receiving ketamine found 62.5% of patients required additional

**Table 4**
Agitation scores and time until control of agitation.

| | n | 0 min (mean ± SD) | 5 min | 10 min | 15 min | Time until control (min) (mean ± SD) |
|---|---|---|---|---|---|---|
| Ketamine | 24 | 4.29 (0.91) | 1.25 (1.73) | 0.71 (1.08) | 0.79 (1.14) | 6.57 (8.65) |
| Midazolam | 19 | 4.58 (0.77) | 2.90 (1.56) | 2.58 (1.54) | 1.95 (1.51) | 14.95 (10.47) |
| Lorazepam | 33 | 4.24 (1.06) | 2.51 (1.71) | 1.85 (1.58) | 1.45 (1.52) | 17.73 (24.78) |
| Haloperidol | 14 | 4.29 (0.91) | 2.79 (1.63) | 2.71 (1.32) | 2.14 (1.66) | 13.43 (15.36) |
| Combo | 10 | 4.80 (0.42) | 3.60 (1.26) | 2.30 (1.83) | 1.10 (1.37) | 23.30 (25.12) |
| p-Value | | 0.386 | 0.001 | <0.001 | 0.032 | 0.107 |

**Table 5**
Redosing of sedative medication.

| | n | Number needing rescue medications | p value |
|---|---|---|---|
| Ketamine | 24 | 14 (58.3%) | |
| Midazolam | 19 | 15 (78.9%) | |
| Lorazepam | 33 | 26 (78.8%) | |
| Haloperidol | 14 | 7 (50.0%) | |
| Combo | 10 | 7 (70%) | 0.199 |

sedating medication [17]. Similarly, 14/24 (58.3%) of our patients given ketamine required redosing, though there was not a significant difference in redosing among groups. Ketamine is unlikely to resolve the underlying processes causing agitation and in this context it is used to gain rapid control of violent patients so that safe medical evaluation can proceed and treatment of the underlying cause can commence.

Only 2/23 (8.7%) of our ketamine patients were intubated, which is significantly lower than in prehospital studies, with rates as high as 63% [23]. A retrospective case series of 32 emergency department patients receiving ketamine for agitation reported no intubations [17]. The ED intubation rate may be lower than prehospital studies due to ED providers' familiarity with the dissociative properties of the medication.

In line with previous studies, which have shown median systolic blood pressure changes from +5 to +17 mm Hg and heart rate changes from 0 to +8 beats per minute [5,17], we found ketamine to have relatively stable hemodynamic effects. It is possible that the agitation-controlling properties of ketamine counteract its sympathetic effects, leading to a relatively neutral hemodynamic profile in this patient population.

### 4.1. Limitations

This was a single center study in a population exhibiting a high percentage of methamphetamine abuse. Data may not be generalizable to populations with different toxicological profiles. It was not possible to randomize patients and so some selection bias may exist. It is important to note though that without randomization, groups were similar in initial agitation scores, gender, race, alcohol abuse, and psychiatric history.

**Table 6**
Change in vital signs in first hour after medication administration (mean ± SD).

| | Initial vitals[a] | Mean change within first hour[b] | p value |
|---|---|---|---|
| Ketamine | | | |
| Pulse rate | 102.3 (25.7) | 92.7 (21.7) | 0.087 |
| Systolic blood pressure | 139.8 (18.7) | 140.3 (24.0) | 0.834 |
| Midazolam | | | |
| Pulse rate | 110.4 (30.0) | 96.9 (22.9) | 0.026 |
| Systolic blood pressure | 129.3 (18.9) | 123.8 (24.8) | 0.226 |
| Lorazepam | | | |
| Pulse rate | 114.7 (32.5) | 109.9 (25.0) | 0.377 |
| Systolic blood pressure | 134.7 (26.5) | 133.4 (26.5) | 0.665 |
| Haloperidol | | | |
| Pulse rate | 104.7 (14.80) | 104.6 (20.9) | 0.974 |
| Systolic blood pressure | 129.2 (24.7) | 144.5 (30.3) | 0.058 |
| Combo | | | |
| Pulse rate | 99.6 (19.1) | 90.5 (12.7) | 0.197 |
| Systolic blood pressure | 140.7 (20.1) | 129.0 (24.7) | 0.195 |

[a] Pulse rates are in beats/minute. Systolic blood pressures are presented in mm Hg.
[b] This represents the mean of the largest change from initial vitals that were documented anytime in the first hour after receiving sedative medication.

While blinded to hypotheses, physicians were not blinded to the medications patients received which may have biased their assessment of time to sedation. The retrospective collection of the secondary outcome variables carries with it the limitations inherent in chart reviews.

Dosing was not uniform and varied among medications making direct comparisons imperfect. Mean medication doses administered were below current recommended doses for ketamine and midazolam.

Our study is limited by its sample size. Although ketamine administration had similar adverse events as other sedating medications, a larger sample is required to reliably confirm its safety profile. The change in vital signs data is limited to what was charted by nursing staff in the first hour after medication administration. This study was not powered to detect differences in adverse events or vital signs.

We also did not account for pre-hospital treatment. It may be possible that some patients received medication prior to presenting to the ED, as is the case with a patient who received naloxone just prior to arrival. Prehospital providers were not able to administer ketamine at the time the study was conducted.

### 4.2. Conclusion

In summary, in highly agitated and violent emergency department patients, significantly fewer patients receiving ketamine as a first line sedating agent were agitated at 5-, 10-, and 15-min. Ketamine appears to be faster at controlling agitation than standard ED medications.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ajem.2017.02.026.

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