# Intubation of Profoundly Agitated Patients Treated with Prehospital Ketamine

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## Abstract

**Background**: Profound agitation in the prehospital setting confers substantial risk to patients and providers. Optimal chemical sedation in this setting remains unclear.

**Objective**: The goal of this study was to describe intubation rates among profoundly agitated patients treated with prehospital ketamine and to characterize clinically significant outcomes of a prehospital ketamine protocol.

**Methods**: This was a retrospective cohort study of all patients who received prehospital ketamine, per a predefined protocol, for control of profound agitation and who subsequently were transported to an urban Level 1 trauma center from May 1, 2010 through August 31, 2013. Identified records were reviewed for basic ambulance run information, subject characteristics, ketamine dosing, and rate of intubation. Emergency Medical Services (EMS) ambulance run data were matched to hospital-based electronic medical records. Clinically significant outcomes are characterized, including unadjusted and adjusted rates of intubation.

**Results**: Overall, ketamine was administered 227 times in the prehospital setting with 135 cases meeting study criteria of use of ketamine for treatment of agitation. Endotracheal intubation was undertaken for 63% (85/135) of patients, including attempted prehospital intubation in four cases. Male gender and late night arrival were associated with intubation in univariate analyses ($\chi^2 = 12.02$; P = .001 and $\chi^2 = 5.34$; P = .021, respectively). Neither ketamine dose, co-administration of additional sedating medications, nor evidence of ethanol (ETOH) or sympathomimetic ingestion was associated with intubation. The association between intubation and both male gender and late night emergency department (ED) arrival persisted in multivariate analysis. Neither higher dose (>5mg/kg) ketamine nor co-administration of midazolam or haloperidol was associated with intubation in logistic regression modeling of the 120 subjects with weights recorded. Two deaths were observed. *Post-hoc* analysis of intubation rates suggested a high degree of provider-dependent variability.

**Conclusions**: Prehospital ketamine is associated with a high rate of endotracheal intubation in profoundly agitated patients; however, ketamine dosing is not associated with intubation rate when adjusted for potential confounders. It is likely that factors not included in this analysis, including both provider comfort with post-ketamine patients and anticipated clinical course, play a role in the decision to intubate patients who receive prehospital ketamine.

## Introduction

Ketamine is a commonly used sedating and anesthetic agent in the hospital setting[1] with a relatively rapid onset of effect (three to eight minutes) after intramuscular (IM) administration. It is used in emergency departments (EDs) to facilitate painful and fear-provoking procedures necessitating moderate sedation, particularly in pediatric patients.[2-6] Previous works demonstrate its efficacy as a prehospital analgesic agent in the setting of severe trauma[7-10] and as a well-tolerated surgical anesthetic in austere and resource-poor settings.[11,12] Despite its frequent use in these settings, the use of ketamine as a first-line agent to control prehospital agitation is not accepted widely.

Profound agitation represents a significant risk to patients and providers alike, and the use of prehospital physical and chemical restraint during transport often is required to maintain the safety of the patient, first responders, and medical staff.[13-15] Case reports[16,17] and laboratory data[18-22] suggest that physical restraint of profoundly agitated individuals may decrease venous return, impair physiologic recovery, and decrease chest wall excursion and minute ventilation. Taken together, these changes suggest impairment in physiologic compensation for the metabolic acidosis incurred by persistent agitation. In the setting of psychomotor stimulation and substance abuse, profoundly agitated patients who are restrained forcefully may thus be at high-risk for cardiovascular collapse.[23] Sedation with classically employed, slower-onset chemical restraints, such as haloperidol and the benzodiazepine sedative-hypnotic class, carries the risk of a delay to adequate sedation that is clinically significant in the setting of often brief ambulance transport.[24]

Ketamine has emerged as a potentially useful agent for the control of subjects with undifferentiated prehospital agitation, but dosing guidelines, safety profile, and efficacy have been described in only a limited fashion. Published case series of ketamine therapy for agitation in the prehospital setting are few,[25,26] although several small case series and individual cases have been reported.[27-30] Preserved respiratory drive classically is described once a ketamine-induced dissociative state is achieved, but little data are available regarding the rate of intubation in this setting. The few large series reported suggest that the rate of intubation among agitated patients treated with prehospital ketamine is higher than that of patients treated with more traditionally accepted sedatives, although time to adequate sedation is more favorable.[31,32] The authors thus sought 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.

## Methods
### Study Design
This was a retrospective cohort study of all patients who received prehospital ketamine for control of profound agitation per a pre-defined Emergency Medical Services (EMS) protocol (Figure 1) and who were transported to an urban county hospital. Exposure to prehospital ketamine from May 1, 2010 through August 31, 2013 was identified by a directed computerized search of the prehospital service database ("SafetyPAD" EMS Information Management System, Open Inc.; Bloomington, Minnesota USA) for all references to "ketamine" during the period reviewed. These episodes of care were matched to hospital records from the date of contact. The governing Office for Human Subjects Research at Hennepin County Medical Center (Minneapolis, Minnesota USA; where the EMS system is based) approved this study.

### Study Setting & Population
The study was conducted at a Level 1 urban trauma center with more than 100,000 annual ED visits from a culturally and linguistically diverse patient population representing over 50 language groups. Prehospital data were provided by a third-service, hospital-operated EMS system which answers over 68,000 calls annually, serves an urban and suburban population of over 1,000,000 residents, and covers more than 200 square miles. On an annual basis, the service responds to over 400 calls coded specifically as "agitation." Some of these episodes of care meet protocol-defined criteria for

"profound" agitation. All ambulances are Advanced Life Support certified and staffed with two paramedics.

### Study Protocol
In May 2010, the EMS service instituted standing orders facilitating ketamine administration by paramedics for control of profound agitation, defined as the patient who displays "active physical violence to himself/herself or others…and usual chemical or physical restraints…may not be appropriate or safely used."[33] In the case of this EMS system, "usual chemical restraint" is attained via IM, intravenous, or intraosseous administration of midazolam (5mg) and/or haloperidol (5-10mg). Ketamine is available to prehospital providers for the management of profoundly agitated patients, as described in Figure 1. It is administered intramuscularly in a dose of 5mg/kg based on estimated body weight. Although rarely applicable, up to 2mg/kg also may be administered intravenously if peripheral vascular access has been obtained.

All individuals ≥18 years of age treated with ketamine for profound agitation in the prehospital setting were eligible for inclusion in the study. Patients known to be pregnant or who were transported to other facilities were excluded from the study. Those who received ketamine purely for analgesic purposes per a parallel EMS protocol for acute pain management were excluded. Therefore, only non-pregnant patients, ≥18 years of age, who received prehospital ketamine for control of profound agitation were included.

Prehospital and electronic hospital medical records were reviewed for each potential study subject identified as having received prehospital ketamine. Indication for prehospital ketamine was noted specifically in a unique data entry field in all EMS run sheets. Cases meeting inclusion criteria were enrolled in the study and evaluated as described in the Measurements and Data Analysis sections. Two authors (PN, EMS fellow and TO, emergency medicine resident physician) jointly abstracted all data from the electronic medical record. Oversight was provided by the EMS medical director (JH). Consensus between the two chart abstractors was achieved in all cases for which interpretation of hospital or prehospital data differed. Vital and laboratory data were abstracted from vital sign flow sheets and laboratory results sections of the electronic medical record; in cases of vital or laboratory derangements reported in provider notes, but not verified in vital sign or laboratory flow sheets, flow sheet data are reported. Physiologically implausible vital signs (eg, diastolic blood pressure greater than systolic blood pressure or temperature of 9.8 degrees Fahrenheit) were excluded following consensus. Data collected during the hospitalization but following ED management was not included in the analysis. Missing data (eg, no temperature recorded) was coded as such. Abstractors reviewed coding and verified consistency of practice on multiple occasions throughout the study.

All prehospital data points (case impression, ketamine dosing and complications, response to ketamine, and additional sedation) were entered electronically into a data collection sheet (Microsoft Excel 2011, Microsoft Corp.; Redmond, Washington USA) and matched by name, date and time of EMS run, and clinical context to the corresponding hospital encounter on the same date and time. In a large majority of cases, prehospital EMS run sheets were available as scanned documents in hospital charts, further verifying appropriate matching.

### Measurements
The paramedic case impression, ketamine dose and route, time of presentation, and additional prehospital sedation (ie, haloperidol

## EMS prehospital profound agitation protocol[30]

**1. If the patient is profoundly agitated with active physical violence to himself/herself or others evident, and usual chemical or physical restraints (section C) may not be appropriate or safely used, consider:**
- Ketamine 5 mg/kg IM (If IV already established, may give 2 mg/kg IV/IO).
- DO NOT attempt to place an IV in a severely combative patient.

2. If ketamine is administered, rapidly move the patient to the ambulance and be prepared to provide:
    a. Respiratory support including suctioning, oxygen, and intubation.
    b. Monitoring of the airway for laryngospasm (presents as stridor, abrupt cyanosis/hypoxia early in sedation period). If laryngospasm occurs perform the following in sequence until the patient is ventilating, then support as needed:
        i. Provide jaw thrust and oxygen.
        ii. Attempt Bag Valve Mask (BVM) ventilation.
        iii. Intubate over gum bougie/tracheal tube introducer with appropriate RSI medications as needed (per applicable service protocols). Cords likely to be closed if not paralyzed thus the need for introducer.
- If hypersecretion is present, consider atropine IV/IO 0.1-0.3 mg IV or 0.5 mg IM.
- If emergence of hallucinations/agitation after administration of ketamine, consider midazolam 2-5 mg IM/IV/IO.

**3. Consider IV access once sedation occurs (if no IV access previously established and ketamine given IM) then administer normal saline wide open up to 1 liter.**

**4. Consider sodium bicarbonate 1 amp IV/IO push.**

**5. Rapid transport at earliest opportunity.**

**Figure 1.** EMS Prehospital Profound Agitation Protocol.
Abbreviations: EMS, Emergency Medical Services; IM, intramuscular; IO, intraosseous; IV, intravenous.

and midazolam) were abstracted from the prehospital database. Because the protocol followed by the prehospital providers mandates an IM dose of ketamine approximating 5mg/kg, this was chosen as a cutoff to assess for exposure to a high (>5mg/kg) or low (≤5mg/kg) ketamine dose for the purpose of analysis. Case impression is assigned by the EMS provider at the point-of-care based on observations made at the scene, often with baseline vital sign measurements, but typically absent advanced diagnostics. Case impressions are the basis on which treatment is initiated prior to arrival at the ED.

Prehospital data points were combined with data abstracted from the subject's medical record, including age, gender, presenting vital signs in the ED, and laboratory data including serum or breath ethanol (ETOH) level, serum bicarbonate, lactate, creatine kinase, venous or arterial pH, and urine toxicology testing (immunoassay followed by high-performance liquid chromatography and mass spectrometry). Prehospital and medical records were reviewed for evidence of clinically significant complications of ketamine administration. Hour of presentation was recorded as a proxy for resources available in the ED. Race could not be abstracted verifiably from the chart retrospectively and thus is

not reported. Where patient weight from the encounter was not recorded immediately, the most proximal weight documented within one month of presentation was used to estimate weight-based ketamine dosing.

Intubation and indication for intubation, where directly referenced, were abstracted from the electronic medical record. No list of uniformly accepted indications for intubation of the agitated patient is utilized at the receiving institution. While it is not standard practice to intubate agitated patients for safety and expeditious evaluation, it is common practice to aggressively treat agitation with chemical restraint and appropriate environmental cuing. Failing these measures, intubation is undertaken in the most refractory cases, particularly those felt to be at risk of secondary complications (eg, rhabdomyolysis, persistent acidemia, or physical injury).

### Data Analysis
Descriptive statistics were employed to characterize the study population. Using the Shapiro-Wilk method at an α of 0.001 and normal quantile plots, data generally were not distributed normally, and thus are presented as medians and interquartile

ranges (IQRs). Univariate analyses describe the association between intubation and baseline demographic and collected clinical data using the Mann-Whitney U test, Pearson's $\chi^2$, or Fisher's exact $\chi^2$ statistic, as appropriate to the data. Logistic regression was used to further evaluate variables associated with intubation. Hosmer-Lemeshow goodness-of-fit $\chi^2$ statistics were calculated subsequently to evaluate acceptable model fit. All data analyses were completed using Stata 12.1 (StataCorp; College Station, Texas USA).

## Results

Prehospital ketamine was administered on 227 occasions during the study period. Of these, 92 were excluded. A single patient with recurrent episodes of encephalopathic behavior was responsible for 38 of 47 exclusions due to EMS transport to a different facility.[34] An additional 33 were excluded due to protocol-driven use of ketamine solely for analgesia, and 12 doses were excluded due to administration to patients less than 18 years of age. A total of 135 episodes of prehospital ketamine administration for profound agitation thus were included for analysis (Figure 2).

Baseline demographic and vital data are presented in Table 1. Overall, 44% (60) of patients presented with tachycardia at or above 120 beats per minute, and 35% (48) presented with Stage 2 systolic hypertension (systolic blood pressure of >160mmHg) or above. Patients were predominantly male (108/135; 80%). In general, patients who were intubated presented with baseline vital signs similar to those who were not intubated. Several records contained incomplete vital data, including systolic blood pressure (1) and weight (15). Of the 15 records without a documented weight, 13 were non-intubated subjects.

The median dose of ketamine was 5.20mg/kg (IQR = 4.59-6.07mg/kg) with weights available in 120 patients. Ketamine doses in excess of 5mg/kg were administered to 70 subjects; a maximum dose of 11.5mg/kg was administered to a patient who did not require intubation. Ketamine dosing did not differ significantly between intubated and non-intubated patients (median 5.25mg/kg and 5.14mg/kg, respectively; Mann-Whitney U-test P = .68). Emergency Medical Service providers reported initial improvement in agitation following ketamine administration in 124/135 (91.8%), no change in 9/135 (6.7%), and worsened agitation in 2/135 (1.5%) of cases.

Endotracheal intubation was undertaken in 85 subjects (63%). Of these, EMS providers attempted intubation in four subjects (2.96%) in the prehospital setting. No cases of pulmonary edema or laryngospasm were verified in the ED charts. Increased oropharyngeal secretions, a known effect of ketamine administration, were not considered clinically important complications for the purpose of this study. The circumstances surrounding prehospital intubations, as well as noted complications of ketamine administration, are characterized in Table 2. Among the four patients in whom prehospital intubation was undertaken, one experienced post-ketamine vomiting and jaw clenching, followed by two failed intubation attempts and placement of a supraglottic airway prior to ED intubation. Another patient experienced transient severe hypoxemia after intubation attempts were frustrated by a strong gag. An oral airway was placed, after which the patient was intubated in the ED. Two more were intubated prehospital, one due to cardiac arrest and the other due to a clinical impression of "coma with an absent gag reflex."

Detailed explanations of the rationale behind the decision to intubate in the ED uniformly were unavailable. Directly referenced
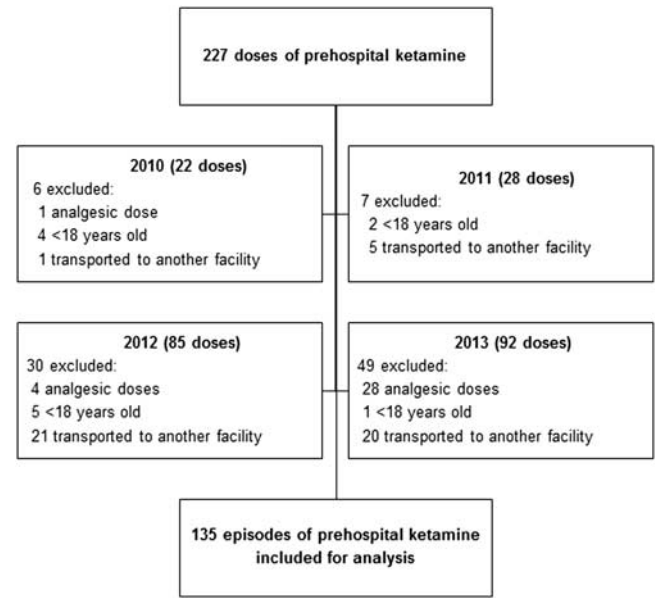
**Figure 2.** Study Flowsheet.

|  | Intubated | Not Intubated |
|---|---|---|
|  | N = 85 | N = 50 |
| Gender (n, %) |  |  |
| Male | 76 (89.4) | 32 (64.0) |
| Female | 9 (10.6) | 18 (36.0) |
| Age | 31 (24-40) | 32 (25-42) |
| Weight (kg)[a] | 85.9 (78.3-97.0) | 87.2 (75.7-97.9) |
| Heart Rate | 119 (103-136) | 118 (107-132) |
| Systolic Blood Pressure (mmHg)[b] | 151.5 (139-174) | 149 (135-259) |
| Respiratory Rate | 20 (16-23) | 20 (16-23) |
| Peripheral Oxygen Saturation (%) | 98 (94-100) | 97 (95-99) |

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**Table 1.** Baseline Characteristics (all data presented as median and interquartile range, unless otherwise noted)
[a] Data missing for 13/50 un-intubated and 2/85 intubated subjects.
[b] Data massing for 1/85 intubated patients (presented to emergency department in arrest).

indications for the procedure included airway protection (69 references); respiratory failure, depression, distress, or apnea (16 references); ongoing agitation or violence (eight references); cardiac arrest (two references); and altered mental status (one reference). A single indication was referenced in 64/85 intubations (75.3%), more than one indication was referenced in 19/85 intubations (22.4%), and no indication was referenced directly in 2/85 intubations (2.4%).

Adjunctive prehospital sedation was administered to 19 patients (14.1%), including midazolam (8/19), haloperidol (1/19),

| Age (years) | Gender | Dose and Route | Prehospital Intubation | Adjunct Sedation | Complication | Notes |
|---|---|---|---|---|---|---|
| 20 | Male | 5.5mg/kg IM | No | ETOH negative | Hypotension | "Hypotension" coded, but lowest recorded blood pressure 180/90 (prehospital) and 118/86 (ED). |
| 19 | Female | 6.5mg/kg IM | Yes | 10 mg IM midazolam ETOH negative | "Coma without gag reflex" | Respiratory depression following ketamine for methamphetamine, "bath salts," and marijuana ingestion. Discharged home the following day. |
| 31 | Female | 4.7mg/kg IM | No | ETOH 334mg/dL | Apneic spell | SpO2 nadir 92%. Bag valve mask ventilated prehospital. |
| 30 | Male | 4.4mg/kg IM | Yes (supraglottic airway after failed attempt) | 10 mg IM haloperidol 5mg IM midazolam ETOH 319mg/dL | Trismus, vomiting, "bradycardic arrest" | Three minutes of prehospital CPR with ROSC; supraglottic airway after failed intubation attempt with vomiting against trismus and resultant severe hypoxia. Diagnosed with frontal subdural hematoma. |
| 22 | Male | 5.4mg/kg IM | Yes (oral airway after failed attempt) | ETOH 218mg/dL | "Irregular bradypnea" | Strong gag reflex precluded prehospital intubation attempts x2 with SpO2 nadir 58%. Intubated in the ED, self-extubated on HD2 and discharged home. |
| 36 | Male | 6.25mg/kg IM | Yes | ETOH not measured | Cardiac arrest | Found severely agitated after lethal overdose of citalopram and clonidine. Ketamine administered per protocol. Subsequently arrested and intubated. Death in ED. |
| 42 | Male | 500mg IM[a] | No | ETOH negative | Cardiac arrest | Multiple seizures throughout the day. Ketamine administered for severe agitation. Several minutes later noted apneic, pulseless. Transported to ED with CPR ongoing. Death in ED. |

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**Table 2.** Prehospital Intubation Cases and Reported Complications of Ketamine Administration in the Prehospital Setting
Note: Prehospital "respiratory depression" is reported in 18 additional patients following ketamine administration. Most EMS run sheets note "suspected hypoxemia" as the basis for intervention. Prehospital treatment commonly included oxygen administration by one or a combination of nasal cannula or facemask (9), bag-valve mask ventilation (8), nasal airway (4), repositioning (2), suctioning (1), and oral airway placement (1). Six of the 21 (29%) respiratory complications had also received IM midazolam alone (n = 3; range 2-10mg) or in combination with haloperidol (n = 3; range 5-10mg).
Abbreviations: CPR, cardiopulmonary resuscitation; ED, emergency department; EMS, Emergency Medical Services; ETOH, ethanol; IM, intramuscular; ROSC, return of spontaneous circulation.
[a] No weight on file.

or both (10/19). Intubation rates were similar across groups receiving any or no adjunctive therapies (68.4% versus 62.1%; Pearson $\chi^2$ P = .595).

Fifty-five patients (40.7%) presented to the ED between the late night hours of 11:00 PM and 7:00 AM (overnight). Intubation occurred in 74.6% (41/55) of overnight patient encounters, compared to 55% (44/80) of daytime patient encounters (Pearson $\chi^2$ P = .021)

Presenting laboratory results are described in Table 3. Intubated patients presented with lower venous pH values (7.25 versus 7.33;

Mann-Whitney U-test P = .018), but laboratory data otherwise were distributed similarly. The urine of 107 patients (79.3%) was sent for toxicological screening. Of these, six (4.4%) tested negative for any detectable substances; evidence of sympathomimetic ingestion was found in the urine of 34 subjects (31.8% of those tested). Cocaine was detected in the urine of 20 patients (18.7%), amphetamines in 19 (17.8%), and phencyclidine in one patient (0.93%). Urine toxicology was positive for both amphetamines and cocaine in six patients (5.6% of those tested).

|  | Intubated | Not Intubated |
|---|---|---|
|  | Median (IQR) | |
| Bicarbonate (mEq/L) | 22 (18-24) | 22 (17-23) |
|  | n = 83 | n = 41 |
| Ethanol (g/dL)[a] | 0.18 g/dL (0.13-0.25) | 0.19 g/dL (0.15-0.26) |
|  | n = 34 | n = 12 |
| Creatine Kinase (IU/L) | 435 (261-948) | 632 (211-1487) |
|  | n = 43 | n = 11 |
| Lactate (mmol/L) | 5.6 (3.4-8.8) | 7.05 (3.9-12.9) |
|  | n = 39 | n = 14 |
| Venous pH[b] | 7.25 (7.13-7.32) | 7.33 (7.29-7.35) |
|  | n = 28 | n = 14 |
| Arterial pH | 7.33 (7.26-7.36) | 7.32 (7.09-7.33) |
|  | n = 22 | n = 5 |

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**Table 3.** Presenting Laboratory Data
[a] Median concentration including those with detectable levels. Among those with *undetectable* ethanol concentrations: Intubated (n = 72) = 0 (0.0-0.18); Not intubated (n = 28) = 0 (0.0-0.17).
[b] Significant difference between groups (Mann-Whitney U-test P < .05).
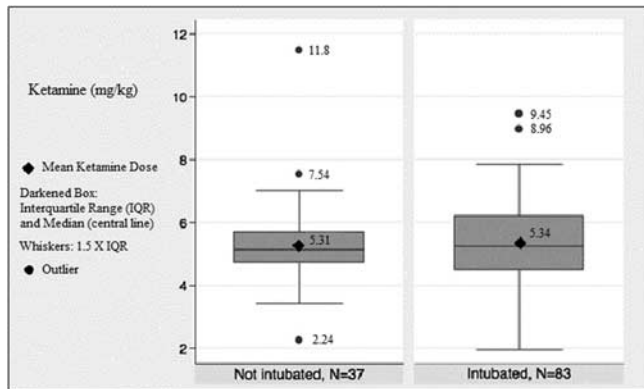


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**Figure 3.** Ketamine Dosage by Intubation Status.

| Impression (n, %) | | |
|---|---|---|
| Agitated/Combative | 45 | (33.8) |
| Behavioral | 33 | (24.8) |
| Substance Abuse | 22 | (16.5) |
| Altered Mentation | 14 | (10.5) |
| Trauma/Injury | 6 | (4.51) |
| Bizarre Behavior | 5 | (3.76) |
| Overdose | 4 | (3.01) |
| Seizure | 2 | (1.50) |
| Hyperglycemia | 1 | (0.75) |
| Cardiac Arrest | 1 | (0.75) |

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**Table 4.** Paramedic Case Impressions

Univariate analyses revealed statistically significant associations between intubation and both male gender (Pearson's $\chi^2$ = 12.02; P = .001) and ED arrival during the overnight shift between 11:00 PM and 7:00 AM (Pearson's $\chi^2$ = 5.34; P = .021). Rates of intubation were similar between subjects receiving low-dose (≤5mg/kg) and high-dose (>5mg/kg) ketamine (72.0% versus 67.1%; Pearson's $\chi^2$ = 0.323; P = .57; Figure 3). Paramedic case impression (Table 4), age >40 years, objective evidence of ETOH or sympathomimetic ingestion on presentation, and prehospital co-administration of midazolam or haloperidol were not associated with intubation.

Logistic regression modeling included binary variables for age (age ≤40 versus >40 years), ketamine dose (≤5mg/kg versus >5mg/kg), gender, co-administration of any prehospital midazolam or haloperidol, and ED arrival time (Table 5). Emergency Medical Service case impression was not included in the adjusted analysis due to inconsistencies in coding of similar presentations and a high likelihood of misclassification bias. Urine toxicology assessments were undertaken on fewer than 80% of subjects, and thus these results were not included in the adjusted analysis. Ethanol concentration similarly was omitted. A total of 120 subjects therefore were included in regression analysis when accounting for those without weights recorded within a month of

| Adjusted Odds Ratio (95%CI) | |
|---|---|
| **Age** | |
| ≤40 years | 1.0 (reference) |
| >40 years | 0.76 (0.29-1.97) |
| **Ketamine Dose** | |
| >5 mg/kg | 1.0 (reference) |
| ≤5 mg/kg | 0.56 (0.24-1.35) |
| **Gender** | |
| Female | 1.0 (reference) |
| Male | 1.91 (1.14-3.21) |
| **ED Arrival Time** | |
| 7:00AM-10:59PM | 1.0 (reference) |
| 11:00PM-6:59AM | 2.57 (1.05-6.27) |
| **Prehospital Midazolam or Haloperidol (any)** | |
| No | 1.0 (reference) |
| Yes | 1.03 (0.30-1.86) |
| Hosmer-Lemeshow test for goodness of fit: $\chi^2$ 5.14 | |

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**Table 5.** Multivariate Analysis of Intubation Rates after Prehospital Ketamine
Abbreviation: ED, emergency department.

their presentation. The association between male gender and intubation persisted in adjusted analysis (odds ratio = 1.91; 95% confidence interval, 1.14-3.21), as did late night arrival (odds ratio = 2.57; 95% confidence interval, 1.05-6.27). Neither age >40 years, ketamine dosing (>5mg/kg), nor co-administration of haloperidol or midazolam was associated with intubation in this model. Binary cut-points of 30 years and 40 years were both modeled due to a bimodal age distribution in the study sample. Neither cut-point suggested an association between age and intubation (data not shown).

Two subjects sustained cardiac arrests shortly after ketamine administration. Both were treated initially with IM ketamine in doses at or near the median study dose. The first, a 36-year-old male, was found breathing sonorously after a reported mixed overdose of citalopram and clonidine. As EMS initiated cares and intravenous access, he became profoundly agitated requiring both physical restraint and chemical sedation. Following 500mg (6.25mg/kg) of ketamine, he was cooperative initially, but subsequently became obtunded. Three minutes after ketamine administration, a cardiac rhythm strip revealed a sinus rhythm with reported T-wave inversions. At nine minutes post-ketamine, the patient developed bradycardia and ultimately sustained a pulseless electrical activity arrest; a right bundle branch block with a prominent (4mm) r-wave in lead aVR was described. Resuscitative efforts were unsuccessful and the patient was pronounced dead 70 minutes after ketamine administration; basic labs were not collected during resuscitation. Emergency physicians cited

pronounced clonidine toxicity as the likely cause of death, but post-mortem clonidine levels were not drawn. Autopsy results revealed quantitative citalopram and amphetamine blood levels of 6,100 nanograms per milliliter (reference level 9-200ng/mL at a daily dose of 30-60mg) and 340ng/mL (reference level 35-110ng/mL at a daily dose of 10-30mg), respectively.[35] The county medical examiner and the medical director of the regional Poison Center independently determined the cause of death to be citalopram and amphetamine toxicity in the setting of chronic substance abuse.

In the second case, EMS was called for a 42-year-old male who had sustained multiple seizures throughout the day following a period of antiepileptic medication refusal. First responders found the patient violent and agitated; EMS noted the same and administered a 500mg dose (approximately 5.15mg/kg based on most recent documented weight of 97kg) of IM ketamine. The patient was transferred to a waiting ambulance where he developed apnea and asystole. Advanced Cardiac Life Support was initiated and resuscitative efforts were continued in the ED where asystole persisted. Initial finger-stick glucose was 222mg/dL, serum sodium 161mEq/L, and serum potassium 6.1mEq/L. Resuscitative efforts failed, and the patient was pronounced dead 57 minutes after ketamine administration. Post-mortem examination revealed tongue hemorrhage consistent with his history of seizure. Further laboratory investigations revealed undetectable serum valproic acid and a urine drug screen with only the nicotine metabolite cotinine; volatile screens were unremarkable. The county medical examiner cited seizure disorder, subtherapeutic anti-seizure medication levels, and atherosclerotic heart disease in the setting of cardiomegaly, hypertension, and a history of substance abuse as the cause of death.

### Discussion
Endotracheal intubation was undertaken for 63% of study subjects, independent of ketamine dose. The case definition of this patient population denotes an immediate danger to themselves and others, and might reasonably impact the decision to undertake aggressive airway management. Thus, profound agitation alone may trigger endotracheal intubation irrespective of choice of sedating medication or response thereto. The degree of agitation identified during the prehospital provider's initial clinical assessment may be articulated incompletely in the medical record, despite being conveyed verbally to the accepting emergency physician. Variables that impact the decision to intubate thus may be incompletely elucidated by this study.

This particularly is highlighted by the case impression coded by prehospital providers. It is subject to limitations inherent to the data that prehospital providers are able to obtain and is based on historical information obtained at the scene. Thus, two patients experiencing very similar pathophysiology may be coded differently. The absence of statistically significant differences in intubation rates across paramedic case impressions likely represents inexact and inconsistent coding, with probable confounding of the causal pathway between the true exposure and the decision to intubate.

Males in this study were more likely than females to be intubated; however, recorded serum pH, serum bicarbonate, evidence of sympathomimetic exposure, and ketamine dose per kilogram body weight were similar across the genders. It is plausible that providers perceived agitated males as a greater danger to providers once patients were admitted to the hospital,

and thus intubated males at a higher rate. Furthermore, communication between prehospital providers and the receiving ED providers may convey a degree of urgency or potential danger unique to a specific patient that is captured inadequately in the medical record.

Patients presenting during the overnight shift were more likely to be intubated than those presenting during the day and evening. Among the 31 staff emergency physicians and fellows who cared for this cohort of patients, two providers accounted for 50.9% (28/55) of overnight encounters, but 65.9% (27/41) of overnight intubations. The same two providers comprised just 7.5% (6/80) of daytime encounters, but 11.4% (5/44) of all daytime intubations. This *post-hoc* finding suggests a provider-dependent practice with respect to airway management in the profoundly agitated patient after prehospital ketamine, and may signify a preference to intubate early when resources are less available (on overnight shifts). Alternately, different providers may variably perceive ketamine-induced dissociation, with some interpreting this as apnea or inadequate airway protection. Finally, it is also plausible that a high rate of intubation overnight represents a perceived safety measure in the absence of a full palette of resources to care for the acutely agitated patient on the hospital floor.

While two providers intubated a majority of profoundly agitated patients who received prehospital ketamine, their practice patterns were not outliers. Among those providers who cared for five or more subjects (n = 10; 32.3%), intubation rates ranged from 0% to 100% (median = 60%; IQR = 25%-92%). These *post-hoc* findings imply that intubation following ketamine administration to control agitation in the prehospital setting – while common and provider-dependent – is not a universal practice, suggesting the need for further study.

The hemodynamic and laboratory parameters of this cohort do not display the degree of derangement characterized in some previously reported cases of profound agitation.[16] However, the improvement of vital sign derangement following prehospital ketamine has also been reported previously.[36] Other reports of severe agitation document substantially more deranged vital parameters, notably in the setting of confirmed sympathomimetic intoxication.[27] In a larger series of patients who met criteria for excited delirium,[14] only 37% (16) of patients presented with tachycardia in excess of 120 beats per minute, and only 7% (3) were hypertensive on presentation to the ED; 5% (2) were hypotensive. Few displayed serum bicarbonate levels of <10mEq/L (three patients; 7.5% of those with labs drawn) or a pH below 7.20 (two patients; 33% of those with labs drawn). By comparison, a large proportion of patients in this study presented with systolic blood pressures greater than or equal to 160mmHg (35%) and with tachycardia at or above 120 beats per minute (44%). Serum bicarbonate was below 20mEq/L in 42 patients (33.9%) and below 10mEq/L in four patients (3.2%), suggesting that this profoundly agitated patient population is comparable to previously described study populations.

The extent of vital and laboratory derangement seen in this study population may represent confounding by medical comorbidities and medications, precluding adequate characterization of agitation severity. Patients receiving beta-adrenergic antagonists for hypertension or anxiety, for example, may be incapable of mounting a tachycardic or hypertensive response that accurately reflects their degree of psychomotor agitation. Therapeutic excess of proserotonergic agents may precipitate dysautonomia, introducing variability into measured hemodynamic parameters.[37] Obstructive lung disease may chronically elevate serum bicarbonate levels, thus leading to an underestimate of the degree of acidosis revealed by this measure in isolation. Finally, a ketamine-induced dissociative state may contribute to a relatively low prevalence of severe hypertension, tachycardia, acidosis, and hyperpyrexia seen in this study following adequate control of neuromuscular agitation.

Few studies characterize the outcomes of agitated patients administered prehospital ketamine. Two small series in unselected patients suggest its utility for a range of clinical needs across a broad age range. In the largest of the two, Svenson & Abernathy reported the administration of ketamine to 40 trauma or medical patients ranging from two months to 75 years of age.[29] The most common indications for the employment of ketamine included analgesia in the setting of hypotension, sedation of the agitated patient without a definitive airway, and analgesia for pain refractory to narcotic pain management, with a reported dosing range from 1mg/kg intravenously to 5mg/kg intramuscularly. No adverse events were reported, although intubation rates following ketamine administration are not described. In a smaller series, Burnett et al describe the ED course of 13 patients in whom ketamine was administered in the prehospital setting for chemical restraint.[24] Of these, one required intubation for recurrent laryngospasm, one was intubated due to intracranial hemorrhage, and five were discharged directly from the ED. Of the 10 non-intubated patients, three were diagnosed by the treating provider as experiencing an emergence reaction. Two more recent series presented in abstract form report high rates of intubation (50% and 38%) and no deaths or laryngospasm in agitated patients administered prehospital ketamine.[31,32]

These results stand in contradistinction to two recent retrospective chart reviews reporting lower intubation rates. Burnett et al report a sample of 49 patients with a range of prehospital ketamine dosing (2.25-9.42mg/kg; mean 5.26mg/kg) that is similar to the patients in the present study.[25] The reported unadjusted rate of intubation of 29% is substantially lower than the rate herein. The mean ketamine dose reported in this study was significantly higher among intubated patients than among patients not requiring intubation; however, the authors note that their univariate model likely does not account for potential confounders. Additionally, although the difference in reported mean ketamine doses to intubated versus non-intubated patients achieved statistical significance, it is unclear that this is a clinically significant finding in a drug classically described in binary terms as "dissociative" or "sub-dissociative." Keseg et al also recently describe EMS-reported improvement in agitation in a cohort of patients administered prehospital ketamine for agitation.[38] Although dosage per kilogram body weight was not described, mean ketamine dose was lower than the mean dose (324mg IM versus 466mg IM) reported in this study. Emergency Medical Services documentation of initially improved agitation was similar (91% in both studies), and improvement in agitation was noted by EMS providers despite eventual ED intubation in at least four patients. The authors similarly point out likely confounders of the relationship between ketamine administration and subsequent intubation, including suspected suicide attempt with polysubstance toxicity and ETOH intoxication. Taken together, these data add depth to a body of knowledge documenting substantial variability in clinically significant outcomes among patients who have received prehospital ketamine.

Finally, the two patients in whom cardiac arrest occurred are of particular concern. Electrocardiographic findings indicative of

severe citalopram toxicity with markedly elevated serum citalopram concentration in the first subject strongly suggest profound serotonin toxicity, a process widely known to produce an agitated state.[37] In the second patient, critical electrolyte dysregulation in the setting of multiple seizures suggest the severity of their illnesses prior to ketamine administration. The degree of agitation encountered by prehospital providers likely is explained by both a post-ictal state and critical hypernatremia, both of which are known to induce alterations in behavior. The medical examiner investigation of both cases found no unifying physiologic mechanism related to ketamine, and in both cases, the critical illness associated with profound agitation strengthened the notion that this patient population must be aggressively medically managed to minimize the potential for poor outcomes. Both cases exemplify the variability of pathology underlying the clinical diagnosis of profound agitation and underscore the inexact correlation of initial case impressions with underlying pathology.

## Limitations

Several important limitations constrain the interpretation of these data. First, this retrospective, single-center, observational study cannot be seen to suggest causality or to apply beyond this center, given the potential for clinical differences between patients transported to this facility and those transported to other facilities after prehospital ketamine. When excluding a single patient who was transported to another facility on 38 occasions, only nine others were excluded due to transport to an alternate facility. Second, this study is subject to limitations inherent to a retrospective review: collected data points cannot be expected to accurately or completely capture the gravity of prehospital agitation, nor can the authors infer a complete articulation of the rationale behind intubation or nuances to the paramedic report that may have influenced the decision to intubate. The high intubation rate may appropriately reflect overall severity of illness, a decision made based on EMS report, anticipated clinical course, available resources, irrespective of the degree of illness severity. It may also reflect variable provider perceptions of the dissociative state induced by ketamine as respiratory failure or failed airway protection. A prospective, ideally multicenter, interventional study of the chemical control of prehospital agitation is needed to validate these findings. Third, the case burden of agitated or combative patients transported by this EMS system likely is underestimated by paramedic case impression coding, as some cases of profound agitation may be coded based on additional contextual data. Finally, additional clinically important outcomes are not captured by this study, notably short- and long-term mortality and duration of intubation following exposure to prehospital ketamine in the setting of profound agitation.

## Conclusions

A large proportion of patients in this series ultimately underwent endotracheal intubation independent of ketamine dosing, although male gender and late night ED arrival were both associated with higher rates of intubation. The basis for observed intubation rates remains unclear, but it appears plausible that indications incompletely articulated in the medical record, including incompletely articulated illness severity, or individual provider practice in the management of post-ketamine patients. Prospective research into both the efficacy and safety of prehospital ketamine and provider interpretation of the ketamine-induced dissociated state is warranted if the rationale for intubating these patients is to be understood completely.

### References

1. Ahern TL, Herring AA, Stone MB, Frazee BW. Effective analgesia with low-dose ketamine and reduced dose hydromorphone in ED patients with severe pain. *Am J Emerg Med*. 2013;31(5):847-851.
2. Adelgais KM, Brown K. Pediatric prehospital pain management: impact of advocacy and research. *Clin Pediatr Emerg Med*. 2014;15(1):49-58.
3. Green SM, Rothrock SG, Harris T, Hopkins GA, Garrett W, Sherwin T. Intravenous ketamine for pediatric sedation in the emergency department: safety profile with 156 cases. *Acad Emerg Med*. 1998;5(10):971-976.
4. Green SM, Denmark TK, Cline J, Roghair C, Abd Allah S, Rothrock SG. Ketamine sedation for pediatric critical care procedures. *Pediatr Emerg Care*. 2001;17(4):244-248.
5. McCarty EC, Mencio GA, Walker LA, Green NE. Ketamine sedation for the reduction of children's fractures in the emergency department. *J None Joint Surg Am*. 2000;82-A(7):912-918.
6. Roback MG, Wathen JE, Bajaj L, Bothner JP. Adverse events associated with procedural sedation and analgesia in a pediatric emergency department: a comparison of common parenteral drugs. *Acad Emerg Med*. 2005;12(6):508-513.
7. Jennings PA, Cameron P, Bernard S, et al. Morphine and ketamine is superior to morphine alone for out-of-hospital trauma analgesia: a randomized controlled trial. *Ann Emerg Med*. 2012;59(6):497-503.
8. Jennings PA, Cameron P, Bernard S. Ketamine as an analgesic in the pre-hospital setting: a systematic review. *Acta Anaesthesiol Scand*. 2011;55(6):638-643.
9. Tran KP, Nguyen Q, Truong XN, et al. A comparison of ketamine and morphine analgesia in prehospital trauma care: a cluster randomized clinical trial in rural Quang Tri Province, Vietnam. *Prehosp Emerg Care*. 2014;18(2):257-264.
10. Wiel E, Zitouni D, Assez N, et al. Continuous infusion of ketamine for out-of-hospital isolated orthopedic injuries secondary to trauma: a randomized controlled trial. *Prehosp Emerg Care*. 2015;19(1):10-16.
11. Paix BR, Capps R, Neumeister G, Semple T. Anesthesia in a disaster zone: a report on the experience of an Australian medical team in Banda Aceh following the Boxing Day Tsunami. *Anaesth Intensive Care*. 2005;33(5):629-634.
12. Mellor AJ. Anesthesia in austere environments. *J R Army Med Corps*. 2005; 151(4):272-276.
13. Maher PJ, Walsh M, Burns T, Strote J. Prehospital resuscitation of a man with excited delirium and cardiopulmonary arrest. *CJEM*. 2014;16(1):80-83.
14. Southall P, Grant J, Fowler D, Scott S. Police custody deaths in Maryland, USA: an examination of 45 cases. *J Forensic Leg Medicine*. 2008;15(4):227-230.
15. Bunai Y, Akaza K, Jiang WX, Nagai A. Fatal hyperthermia associated with excited delirium during arrest. *Leg Med (Tokyo)*. 2008;10(6):306-309.
16. Hick JL, Smith SW, Lynch MT. Metabolic acidosis in restraint-associated cardiac arrest: a case series. *Acad Emerg Med*. 1999;6(3):239-243.
17. O'Halloran RL, Lewman LV. Restraint asphyxiation in excited delirium. *Am J Forensic Med Pathol*. 1993;14(4):289-295.
18. Strote J, Walsh M, Auerbach D, Burns T, Maher P. Medical conditions and restraint in patients experiencing excited delirium. *Am J Emerg Med*. 2014;32(9): 1093-1096.
19. Chan TC, Neuman T, Clausen J, Eisele J, Vilke GM. Weight force during prone restraint and respiratory function. *Am J Forensic Med Pathol*. 2004;25(3):185-189.
20. Ho JD, Dawes DM, Moore JC, Caroon LV, Miner JR. Effect of position and weight force on inferior vena cava diameter – implications for arrest-related death. *Forensic Sci Int*. 2011;212(1-3):256-259.
21. Chan TC, Vilke GM, Neuman T, Clausen JL. Restraint position and positional asphyxia. *Ann Emerg Med*. 1997;30(5):578-586.
22. Reay DT, Howard JT, Fligner CL, Ward RJ. Effects of positional restraint on oxygen saturation and heart rate following exercise. *Am J Forensic Med Pathol*. 1988; 9(1):16-18.
23. Chan TC, Vilke GM, Neuman T. Reexamination of custody restraint position and positional asphyxia. *Am J Forensic Med Pathol*. 1998;19(2):201-205.
24. Isenberg DL, Jacobs D. Prehospital Agitation and Sedation Trial (PhAST): a randomized control trial of intramuscular haloperidol versus intramuscular midazolam for the sedation of the agitated or violent patient in the prehospital environment. *Prehosp Disaster Med*. 2015;30(5):491-495.

25. Burnett AM, Salzman JG, Griffith KR, Kroeger B, Frascone RJ. The emergency department experience with prehospital ketamine: a case series of 13 patients. *Prehosp Emerg Care*. 2012;16(4):553-559.

26. Burnett AM, Peterson BK, Stellpflug SJ, et al. The association between ketamine given for prehospital chemical restraint with intubation and hospital admission. *Am J Emerg Med*. 2015;33(1):76-79.

27. Hick JL, Ho JD. Ketamine chemical restraint to facilitate rescue of a combative "jumper." *Prehosp Emerg Care*. 2005;9(1):85-89.

28. Ho JD, Smith SW, Nystrom PC, et al. Successful management of excited delirium with prehospital ketamine: two case examples. *Prehosp Emerg Care*. 2013;17(2):274-279.

29. Pritchard A, LeCong M. Ketamine sedation during air medical retrieval of an agitated patient. *Air Med J*. 2014;33(2):76-77.

30. Svenson JE, Abernathy MK. Ketamine for prehospital use: new look at an old drug. *Am J Emerg Med*. 2007;25(8):977-980.

31. Iwanicki JL, Barrett W, Saghafi O, et al. Prehospital ketamine for excited delirium in the setting of acute drug intoxication. *Clin Toxicol*. 52(7):685 (Abstract #9).

32. Cole JB, Nystrom PC, Orozco BS, et al. A prospective study of ketamine versus haloperidol for severe prehospital agitation. *Clin Toxicol*. 53(7):642 (Abstract #7).

33. Hennepin County EMS System. Advanced Life Support Protocols. Emergency Medical Services Planning and Regulation. Web site. http://www.hennepin.us/business/work-with-henn-co/ems-planning-reg. Accessed September 17, 2014.

34. Olives TD, Nystrom PN, Ho JD, Cole JB. A patient administered prehospital ketamine on 20 separate occasions. *Clin Toxicol*. 2013;51:675.

35. NMS Labs. *Sample Report Amphetamines Panel (8600B)*. Willow Grove, Pennsylvania USA: NMS Labs; 2014. Robert A. Middleberg, Laboratory Director.

36. Burnett AM, Watters BJ, Barringer KW, Griffith KR, Frascone RJ. Laryngospasm and hypoxia after intramuscular administration of ketamine to a patient in excited delirium. *Prehosp Emerg Care*. 2012;16(3):412-414.

37. Boyer EW, Shannon M. The serotonin syndrome. *NEJM*. 2005;352(11):1112-1120.

38. Keseg D, Cortez E, Rund D, Caterino J. The use of prehospital ketamine for control of agitation in a metropolitan firefighter-based EMS system. *Prehosp Emerg Care*. 2015;19(1):110-115.