Prehospital Ketamine Administration for Excited Delirium with Illicit Substance Co-Ingestion and Subsequent Intubation in the Emergency Department

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Abstract

Introduction: Excited delirium, which has been defined as combativeness, agitation, and altered sensorium, requires immediate treatment in prehospital or emergency department (ED) settings for the safety of both patients and caregivers. Prehospital ketamine use is prevalent, although the evidence on safety and efficacy is limited. Many patients with excited delirium are intoxicated with illicit substances. This investigation explores whether patients treated with prehospital ketamine for excited delirium with concomitant substance intoxication have higher rates of subsequent intubation in the ED compared to those without confirmed substance usage.

Methods: Over 28 months at two large community hospitals, all medical records were retrospectively searched for all patients age 18 years or greater with prehospital ketamine intramuscular (IM) administration for excited delirium and identified illicit and prescription substance co-ingestions. Trained abstractors collected demographic characteristics, history of present illness (HPI), urine drug screens (UDS), alcohol levels, and noted additional sedative administrations. Substance intoxication was determined by UDS and alcohol positivity or negativity, as well as physician HPI. Patients without toxicological testing or documentation of substance intoxication, or who may have tested positive due to ED sedation, were excluded from relevant analyses. Subsequent ED intubation was the primary pre-specified outcome. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to compare variables.

Results: Among 86 patients given prehospital ketamine IM for excited delirium, baseline characteristics including age, ketamine dose, and body mass index were similar between those who did or did not undergo intubation. Men had higher intubation rates. Patients testing positive for alcohol, amphetamines, barbiturates, benzodiazepines, ecstasy, marijuana, opiates, and synthetic cathinones, both bath salts and flakka, had similar rates of intubation compared to those negative for these substances. Of 27 patients with excited delirium and concomitant cocaine intoxication, nine (33%) were intubated compared with four of 50 (8%) without cocaine intoxication, yielding a 5.75 OR (95%, CI 1.57 to 21.05; P = .009).

Conclusion: Patients treated with ketamine IM for excited delirium with concomitant cocaine intoxication had a statistically significant 5.75-fold increased rate of subsequent intubation in the ED. Amongst other substances, no other trends with intubation were noted, but further study is warranted.

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Introduction

Excited delirium is defined by combativeness, agitation, and altered sensorium. This adrenergic state may result from psychiatric conditions, recreational drug use, or rarely medical conditions.\(^1\) Among the most serious deleterious consequences are rhabdomyolysis, hyperthermia and sudden death.\(^1\)

In the prehospital and emergency department (ED) settings, excited delirium requires immediate treatment for the safety of both patients and their caregivers. In the past, physical restraint was the predominant method used to control the patient during transport.\(^2\) Safety issues for patients and caregivers necessitated a re-evaluation of the use of physical restraints.\(^1\) Initially, treatments for agitation including antipsychotics and benzodiazepines were used, but more recently, prehospital ketamine has become common.\(^3\)\(^-\)\(^6\)

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that produces analgesia at lower doses but may precipitate general anesthesia with a dissociative state at higher doses.\(^6\) Routes of administration include intraosseous (IO), intramuscular (IM), intranasal (IN), and intravenous (IV). Emergency Medical Services (EMS) typically use the IM route due to the difficulty in obtaining IV access in patients with excited delirium. The onset of action is approximately three to four minutes when given IM and approximately 30 seconds when given IV.\(^6\) In addition to rapid onset of action, ketamine generally maintains airway reflexes and generally has a favorable side effect profile. The higher doses of ketamine IM have a more rapid onset and offer obvious advantages to EMS providers.\(^6\)

Ketamine is safe and well-tolerated when administered in a controlled environment for procedural sedation, as patients rarely lose their airway or respiratory drive.\(^6\) However, co-ingestants may alter the properties of the drug. While there have been prior studies showing the safety of utilizing large doses of ketamine intramuscularly to treat agitation, a significant subset of these patients require intubation.\(^7\)\(^-\)\(^8\) Risk factors for respiratory arrest and intubation have not been well-established.

In one related study with prehospital use of ketamine for excited delirium, patients subsequently intubated in the ED tended to have higher temperatures and lower Glasgow Coma Scale (GCS) scores compared to those not intubated, although there was no control for possible confounding by co-ingestants.\(^7\) It is known that many patients with excited delirium are intoxicated on illicit substances. Therefore, using data-derived hypothesis generation, this study builds upon the previous\(^7\) and describes the association between prehospital ketamine administration in excited delirium with concomitant illicit and prescription substance intoxication and subsequent ED intubation.

Methods

This was a retrospective chart review from January 1, 2017 through April 30, 2019 of patients treated at two South Florida (USA) community hospitals with a combined annual volume of 81,000. This research was approved by the institutional review boards of Florida Atlantic University (Boca Raton, Florida USA; study #1342058) and Baptist Health South Florida (Miami, Florida USA; study #1446400). This study collected new data about patients enrolled in a prior study, whereby the electronic medical records of all ED encounters were queried by the medical records department for the word “ketamine.”\(^7\)\(^7\) Using this previously generated report, all patient charts were individually screened by a medically trained co-investigator, blinded to the hypotheses, for the prehospital use of ketamine for excited delirium. Inclusion criteria were age 18 years or greater and ketamine IM administration for excited delirium by prehospital providers. Patients were excluded if ketamine was used by EMS for post-intubation sedation, pain control, or as an induction agent. The EMS protocol for excited delirium, defined as a patient presenting with bizarre/aggressive behavior, consisted of: ketamine 400mg IM, may repeat one time as needed, with maximum single dose 400mg IM; if patient begins to wake up: midazolam 2.5mg IV/IO slowly over two minutes or midazolam 5mg IN/IM.

After initial screening, a different medically trained co-investigator performed a chart review of the hospital records of eligible patients. Variables collected included age, gender, comorbidities, ketamine dose, height, weight, laboratory values, substance use, need for intubation, and index visit mortality. Laboratory values collected were initial creatine phosphokinase, creatinine, sodium, lactic acid, ethanol level, and urine drug screen (UDS) immunoassay results. Qualitative analysis of urine toxicology included amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, opiates, and phencyclidine (PCP). History of present illness (HPI) documentation from the ED physician notes was evaluated for patient use of illicit substances (barbiturates, cocaine, ecstasy, heroin, hyseric acid diethylamide [LSD], marijuana, methamphetamines, PCP, and synthetic cathinones [bath salts/flakka]); prescription drugs of abuse (benzodiazepines, gabapentinoids, hypnotics, opioids, and stimulants); and alcohol use. Both EMS/ED administration of additional sedatives were recorded (benzodiazepines, typical antipsychotics, atypical antipsychotics, and opioids). The primary outcome variable, whether the patient required intubation, was determined based on review of ED physician notes. Index visit mortality was determined based on hospital disposition. These data were reviewed by a second investigator to confirm data extraction accuracy and minimize bias.\(^9\) All study data were entered into Research Electronic Data Capture (REDCap), a Health Insurance Portability and Accountability Act (HIPAA)-compliant web-based data management system with real-time error checking.

Analyses of toxicological laboratory data, first without and second including HPI data, were performed using SPSS Statistics Version 27 (IBM Corporation; Armonk, New York USA). In the first analysis, co-ingestant variables were defined by either UDS results (positive or negative) or blood alcohol levels (a level ≥100mg/dL or greater was defined as positive). Patients without UDS or blood alcohol level testing were excluded from this analysis. For the second analysis, combined with the toxicological data, if a patient was on an illicit substance based on the HPI, then that substance was defined as positive and all other illicit substances were defined as negative. If an illicit substance was documented as negative, then that substance was defined as negative. For prescription drugs of abuse and alcohol abuse, the same methodology was followed. Any patients that had unknown or not documented illicit substance use, prescription drug abuse, or alcohol abuse in the HPI were excluded from the respective analyses. Patients who used heroin per the illicit substance HPI, used an opioid per the prescription drugs of abuse HPI, or opiates on UDS were combined. Methamphetamines, stimulants, and amphetamines were similarly combined. Since UDS benzodiazepines positivity may reflect both patient abuse as well as medical treatment, an additional analysis was performed excluding patients who received benzodiazepines by EMS or in the ED. To compare patients intubated to those who were not for each of the ingestants, odds ratios (OR) were used.
as measures of effect with 95% confidence intervals (CI). Fisher’s Exact Test was used to compare proportions, while Student’s T-test was used to compare means.

Results

Of the 86 patients enrolled in the study, 61 had blood alcohol levels tested, 62 had UDS testing performed, 61 had HPI of alcohol use documented, and 15 had HPI with prescription drug abuse documented. Baseline characteristics including age, ketamine dose, and body mass index, defined as weight in kilograms divided by height in meters squared, were similar between patients who did or did not undergo intubation (Table 1). Male gender was significantly associated three-fold with increased rate of intubation (26% male versus 9% female; \( P = .042 \)). There were no deaths during index hospitalization. Table 1 shows that creatinine was significantly higher and sodium significantly lower in the group requiring intubation.

Of the 62 patients who had a UDS performed, patients positive for cocaine were significantly more likely to be intubated than those negative for cocaine (36% versus 10%; \( OR = 5.14; 95\% CI, 1.33 to 19.83 \)). Patients positive for benzodiazepines also had a higher rate of intubation (53% versus 7%; \( OR = 15.75; 95\% CI, 3.48 to 71.27 \)), though this association became non-significant after excluding patients who were treated with benzodiazepines during their EMS/ED care (20% versus 7%; \( OR = 3.50; 95\% CI, 0.29 to 41.99 \)). There was no difference for patients who had any other illicit substance positivity based on UDS testing (Table 2). Alcohol levels of patients intubated (51mg/dL; standard deviation [SD] = 115) versus not intubated (99mg/dL; SD = 150) were not significantly different (\( −48\text{mg/dL difference; } 95\% \text{ CI, } −138 \text{ to } 42; \text{ P} = .289 \)).

When combining HPI and laboratory data, there were similar trends to the analyses of laboratory data alone. Table 3 shows that 27 patients had suspected cocaine intoxication. Among these, nine were intubated (33%) compared with only four of the 50 (8%) without cocaine intoxication (\( OR = 5.75; 95\% CI, 1.57 to 21.05 \)). There were no patients taking gabapentinoids, LSD, or PCP. Among the remaining substances, there were limited numbers of patients for amphetamines, barbiturates, ecstasy, marijuana, opiates, and synthetic cathinones (Table 3).

Discussion

These data indicate that patients given prehospital ketamine IM for excited delirium with concomitant cocaine intoxication had a significant 5.75-fold higher risk of subsequent intubation in the ED. Of 62 who had a UDS performed, 35% tested positive for cocain...

### Table 1. Patient Characteristics by ED Intubation

|                | Intubated | Not Intubated | Difference (95% CI) | P Value |
|----------------|-----------|---------------|---------------------|---------|
| Age (years)    | 39        | 44            | −5 (−16 to 6)       | .352    |
| Gender, n (%)  |           |               |                     | .042    |
| Male           | 10 (26%)  | 29 (74%)      | 3.71 (1.06 to 12.96) | .042    |
| Female         | 4 (9%)    | 43 (91%)      |                     |         |
| Ketamine Dose (mg) | 339    | 351            | −11 (−72 to 50)     | .711    |
| BMI (kg/m²)    | 25.8      | 25.2          | −0.6 (−3.49 to 2.1) | .631    |
| CPK (U/L)      | 1027 (1476) | 588 (556)    | 439 (−423 to 1302) | .293    |
| Creatinine (mg/dL) | 1.34 (0.57) | 1.04 (0.32) | 0.30 (0.08 to 0.52) | .009    |
| Sodium (mEq/L) | 137 (3.8) | 139 (3.7)     | −2 (−4.6 to −0.2)  | .035    |
| Lactic Acid (mmol/L) | 4.5 (4.5) | 3.7 (4.0) | 0.8 (−2.7 to 4.2) | .644    |

### Table 2. Substance Co-Ingestion Positivity using Laboratory Data by ED Intubation

| Substance | Total, n | Intubated, n (%) | Unintubated, n (%) | OR (95% CI) | P Value |
|-----------|----------|------------------|--------------------|-------------|---------|
| Alcohol   | 18       | 2 (11%)          | 11 (63%)           | 0.36 (0.07 to 1.84) | .310    |
| Amphetamine | 3        | 2 (67%)         | 5 (17%)            | 9.80 (0.81 to 118.79) | .093    |
| Barbiturate | 2       | 1 (50%)         | 5 (20%)            | 4.46 (0.26 to 76.85) | .352    |
| Benzodiazepine | 17    | 9 (53%)         | 8 (47%)            | 15.75 (3.48 to 71.27) | <.001 |
| Benzodiazepine | 5       | 1 (20%)         | 4 (40%)            | 3.50 (0.29 to 41.99) | .353    |
| Cocaine   | 22       | 5 (24%)          | 17 (76%)           | 1.52 (0.42 to 5.53) | .520    |
| Marijuana | 21       | 5 (26%)          | 16 (74%)           | 1.84 (0.50 to 6.76) | .487    |
| Opiates   | 19       | 5 (26%)          | 14 (74%)           | 5.14 (1.33 to 19.83) | <.001 |
| PCP       | 0        | 0 (0%)           | 62 (100%)          | 5.04 (1.35 to 18.90) | .017    |

Abbreviations: BMI, body mass index; CPK, creatine phosphokinase; CI, confidence interval.

* Odds ratio (95% CI).

* Overall benzodiazepine results.

* Excludes EMS/ED administration.
Table 3. Substance Co-Ingestion Positivity using Combined HPI and Laboratory Data by ED Intubation

| Substance | Co-Ingestion Positive, n (%) | Intubated, n (%) | OR (95% CI) | P Value |
|-----------|-------------------------------|------------------|-------------|---------|
| Alcohol   | 33 (9%)                       | 3 (9%)           | 0.37 (0.09 to 1.47) | .220 |
| Amphetamine| 4 (50%)                       | 2 (50%)          | 5.82 (0.74 to 45.73) | .124 |
| Barbiturate| 2 (50%)                       | 1 (50%)          | 5.25 (0.31 to 89.83) | .311 |
| Benzodiazepine | 17 (53%)               | 9 (53%)          | 18.75 (4.16 to 84.43) | <.001 |
| Cocaine   | 27 (33%)                      | 9 (33%)          | 5.75 (1.57 to 21.05) | .009 |
| Ecstasy   | 1 (0%)                        | 0 (0%)           | 5.75 (1.57 to 21.05) | .009 |
| Gabapentinoids | 0 (0%)                 | 0 (0%)           | 5.75 (1.57 to 21.05) | .009 |
| Hypnotics | 1 (0%)                        | 0 (0%)           | 5.75 (1.57 to 21.05) | .009 |
| LSD       | 0 (0%)                        | 0 (0%)           | 5.75 (1.57 to 21.05) | .009 |
| Marijuana | 23 (22%)                      | 5 (22%)          | 1.60 (0.46 to 5.54) | .513 |
| Opiates   | 23 (26%)                      | 6 (26%)          | 2.47 (0.73 to 8.39) | .183 |
| PCP       | 0 (0%)                        | 0 (0%)           | 2.47 (0.73 to 8.39) | .183 |
| Synthetic Cathinones | 8 (25%)       | 2 (25%)          | 1.63 (0.28 to 9.41) | .627 |

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