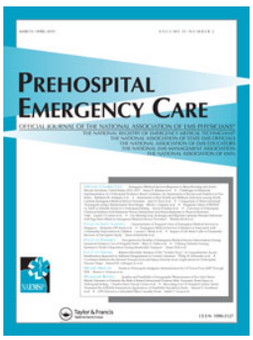

Prehospital Emergency Care

ISSN: 1090-3127 (Print) 1545-0066 (Online) Journal homepage: https://www.tandfonline.com/loi/ipec20

# Outcomes of Prehospital Chemical Sedation With Ketamine Versus Haloperidol and Benzodiazepine or Physical Restraint Only

Laurel O'Connor, Matthew Rebesco, Conor Robinson, Karen Gross, Andrew Castellana, Mark J. O'Connor & Marc Restuccia

**To cite this article:** Laurel O'Connor, Matthew Rebesco, Conor Robinson, Karen Gross, Andrew Castellana, Mark J. O'Connor & Marc Restuccia (2019) Outcomes of Prehospital Chemical Sedation With Ketamine Versus Haloperidol and Benzodiazepine or Physical Restraint Only, Prehospital Emergency Care, 23:2, 201-209, DOI: 10.1080/10903127.2018.1501445

**To link to this article:** https://doi.org/10.1080/10903127.2018.1501445

View supplementary material

Published online: 27 Aug 2018.

Submit your article to this journal

Article views: 1749

View related articles

View Crossmark data

Citing articles: 7 View citing articles

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ipec20

Check for updates

# Outcomes of Prehospital Chemical Sedation With Ketamine Versus Haloperidol and Benzodiazepine or Physical Restraint Only

Laurel O'Connor, MD, Matthew Rebesco, MD, Conor Robinson, BS, Karen Gross, EMT-P, Andrew Castellana, BA, EMT-P, Mark J. O'Connor, MD, Marc Restuccia, MD, FACEP, FAAEM

Abstract

**Objective:** The goal of this study is to describe complications and outcomes of prehospital ketamine use for agitation as compared to other methods of physical or chemical restraint such as haloperidol plus benzodiazepine or physical restraint only. **Methods:** We conducted a single-center retrospective review of patient encounters in which restraint was administered in the prehospital setting. At the beginning of our study window, only physical restraint was available to paramedics managing agitated patients but subsequently, haloperidol and benzodiazepines were introduced, followed by ketamine 2 years later. By comparing patients before and after each transition, we divided subjects into 3 cohorts based on restraint type: physical restraint, haloperidol plus benzodiazepine, and ketamine. Demographic data were collected, and outcome measures included intubation rate, need for additional physical or chemical restraint, emergency department (ED) length of stay, need for hospital admission, and employee injury. **Results:** Of 214 subjects included in the study, 95 patients were administered ketamine, 68 received haloperidol and benzodiazepine, and 51 were physically restrained. Eleven of the patients (11.6%) who received ketamine were intubated. Compared to patients who received haloperidol plus benzodiazepine, patients who received ketamine were more likely to be intubated (odds ratio [OR] = 8.77, 95% confidence interval [CI], 1.10–69.68) and were more likely to require additional chemical restraint when compared to haloperidol/benzodiazepine or physical restraint only (OR =2.94, 95% CI, 1.49–5.80, and OR =2.15, 95% CI, 1.07–4.31, respectively). There were no differences between the 2 chemical sedation groups in terms of ED length of stay or hospital admission rate. **Conclusions:** This study demonstrates a lower intubation rate in patients administered ketamine than prior literature in association with a lower weight-based dosing regimen. Ketamine use was correlated with a higher frequency of intubation and a greater need for additional chemical restraint when compared with other restraint modalities, though exogenous factors such as provider preference may have impacted this result. There was no difference in ED length of stay or admission rate between the ketamine and haloperidol plus benzodiazepine groups. Further prospective study is needed to determine whether there is a subset of patients for whom ketamine would be beneficial compared to other therapies.
**Key words:** agitated delirium; ketamine; restraint; sedation

PREHOSPITAL EMERGENCY CARE 2019;23:201–209

## Introduction

Prehospital providers are often faced with the task of managing and safely transporting patients who are agitated due to chemical, organic, or psychiatric pathologies. Combative patients pose a physical hazard to providers, and they put themselves at risk for accidental injury or complications associated with restraint (1, 2). Such complications have been described extensively in the prehospital literature and include asphyxiation, hyperthermia, heat stroke, and even death (3). Excited delirium syndrome (ExDS) can be exacerbated by physical restraint and is potentially lethal; it results in mortality with little warning if not appropriately identified and treated (4–6). Chemical restraints are recommended for all patients exhibiting signs or symptoms of ExDS for the safety of patients and providers (7). Chemical restraints do, however, have their own adverse effects and can cause complications even when administered in appropriate doses. Therefore, optimizing the effectiveness and safety of chemical restraint administration in the prehospital

Received May 3, 2018 from Department of Emergency Medicine, Boston Medical Center, Boston, Massachusetts (LOC); Department of Emergency Medicine, University of Massachusetts Medical School, Worcester, Massachusetts (MR, CR, KG, AC, MR); Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts (MJO). Revision received July 12, 2018; accepted for publication July 13, 2018.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The authors have no conflicts of interest to report.

Address correspondence to Laurel O'Connor, MD, Department of Emergency Medicine, Boston Medical Center, One Boston Medical Center Place, Boston, MA 02118, USA. E-mail: laurelcarenoconnor@gmail.com

Supplemental data for this article can be accessed on the publisher's website.

© 2018 National Association of EMS Physicians

doi:10.1080/10903127.2018.1501445

setting is vital for ensuring the safety of both providers and patients.

Ketamine is increasingly being used as a chemical restraint in prehospital and hospital settings for ExDS (8–13). It is fast-acting, effective, and considered safe for most patients to provide relief from agitation caused by psychiatric or organic pathology. An uncommon but significant adverse effect of ketamine is the need for intubation due to poor airway protection, laryngospasm, or apnea (14). Other adverse effects of ketamine include hypersalivation and emergence reactions, which may be difficult to differentiate from co-ingestant intoxication (14). Existing alternatives to ketamine for chemical restraint include haloperidol and benzodiazepines (15). These medications, however, have a slower onset than ketamine and have their own side effects, such as extrapyramidal symptoms, long QT syndrome, and respiratory depression (11, 15). Respiratory depression is a particular concern for benzodiazepines because they act synergistically with common co-ingestants such as ethanol. In the prehospital setting, time from administration to adequate sedation is a priority, thus making ketamine an appealing option.

Prior studies have demonstrated the effectiveness of prehospital ketamine administration for agitation but have also demonstrated an unfavorable side effect profile, including very high intubation rates ranging from 23% to 57% (8–10, 12, 13). The vast majority of the intubations reported in this body of literature occurred in the emergency department (ED) and not in the prehospital setting. In this study, we directly compare patients who were administered ketamine with those who were administered haloperidol and benzodiazepines or physical restraint alone in terms of adverse effects such as a need for intubation, impact on length of stay and disposition, rates of staff injury, need for further restraint, and other documented complications of administration.

# METHODS

## Setting and Participants

This study was conducted at a large urban academic medical center. Consecutive subjects 18 years of age or older were considered for inclusion, regardless of presenting complaint, if they were transported to the hospital by the hospital-based emergency medical services (EMS) provider and were administered any standing-order intervention for combative or agitated behavior. Subjects were treated between January 2014 and February 2018. Standing-order interventions available to the paramedic service changed over this time period. Initially, only physical restraint was available. Then in November 2014, intramuscular haloperidol and benzodiazepine (lorazepam or midazolam) became available to the paramedics and, finally, in November 2016, intramuscular ketamine was added. During the ketamine administration time period, the hospital-based service described in this study was the only service with standing orders for ketamine transporting patients to the study site, so no patients transported by any other service received prehospital ketamine. The protocol in place for the EMS service during the time frame of the study directed that ketamine could be administered at the discretion of providers to agitated patients aged 18 or older at a dose of 4 mg/kg based on estimated weight. No other specific guidelines governed contraindications or restriction of use.

The physical restraints utilized were either handcuffs applied with assistance from law enforcement or soft wrist and ankle restraints carried by the EMS providers. All subjects who were administered haloperidol and benzodiazepine were administered 5 mg of haloperidol intramuscularly and between 2 and 4 mg of midazolam or lorazepam.

Encounters during which the qualifying medications were not administered for restraint in the setting of agitation or combativeness (for example, intubation induction, analgesia, anxiolysis, etc.) were excluded from this study, as were charts where physical restraint was applied as a matter of protocol for noncombative patients in police custody. Charts of patients transported to facilities outside of the medical center's system were excluded, including 7 who received prehospital ketamine, because their ED course could not be extracted. In total, 219 charts were identified as potentially meeting qualifying parameters for extraction and 214 charts were extracted. Five charts had to be omitted from extraction because the patient was identified in the prehospital patient care record (PCR) under an alias that could not be reconciled with a real identity in the hospital electronic medical record (EMR) and therefore the ED course could not be documented.

We intentionally extracted charts from 3 discrete time periods in a pre–post model because we wanted to compare the group of patients who received ketamine to historical cohorts. We excluded patients who received haloperidol and benzodiazepine during the time period in which ketamine was available because we felt that these patients represented a unique subgroup. They were deliberately not administered ketamine at the discretion of the prehospital providers for a variety of reasons (age, physical exam findings, etc.) and therefore it is possible that their demographics differed from the

Table 1. Descriptive characteristics

| | Ketamine (n = 95) | Haloperidol + Benzodiazepine (n = 68) | Physical (n = 51) | Ketamine vs. Haloperidol + Benzodiazepine p Value | Ketamine vs. Physical p Value |
|---|---|---|---|---|---|
| Age, years | | | | 0.788 | 0.004 |
| Mean | 34.2 | 35.4 | 42.7 | | |
| Median | 32 | 34 | 42 | | |
| Range | 18, 63 | 18, 78 | 19, 86 | | |
| Gender | | | | | |
| Male | 56 (58.9%) | 47 (69.1%) | 29 (56.9%) | 0.245 | 0.946 |
| Female | 39 (41.1%) | 21 (30.9%) | 22 (43.1%) | | |
| Weight, kg | | | | 0.406 | 0.857 |
| Mean | 82.2 | 79.9 | 80.9 | | |
| Median | 79.4 | 79.3 | 78.8 | | |
| Range | 50, 136 | 49, 136 | 48, 116 | | |
| Comorbidities | | | | | |
| COPD | 3 (3.2%) | 1 (1.5%) | 0 (0%) | 0.863 | 0.503 |
| Asthma | 10 (10.5%) | 10 (14.7%) | 6 (11.8%) | 0.576 | 1 |
| CAD | 0 (0%) | 1 (1.5%) | 2 (3.9%) | 0.866 | 0.231 |
| HTN | 10 (10.5%) | 10 (14.7%) | 11 (21.6%) | 0.576 | 0.118 |
| CHF | 1 (1.1%) | 0 (0%) | 1 (2.0%) | 1 | 1 |
| DM | 6 (6.3%) | 5 (7.4%) | 6 (11.8%) | 1 | 0.408 |
| Other | 13 (13.7%) | 23 (33.8%) | 11 (21.6%) | 0.004 | 0.321 |
| Co-ingestions | | | | | |
| Alcohol | 37 (38.9%) | 27 (39.7%) | 29 (56.9%) | 1 | 0.058 |
| Cannabis | 4 (4.2%) | 5 (7.4%) | 2 (3.9%) | 0.604 | 1 |
| Cocaine | 14 (14.7%) | 7 (10.3%) | 0 (0%) | 0.55 | 0.009 |
| Opioids | 16 (16.8%) | 11 (16.1%) | 2 (3.9%) | 1 | 0.046 |
| Other | 14 (14.7%) | 10 (14.7%) | 5 (9.8%) | 1 | 0.558 |
| None | 20 (21.1%) | 7 (10.3%) | 10 (19.6%) | 0.108 | 1 |
| Unknown | 22 (23.2%) | 18 (26.5%) | 8 (15.7%) | 0.764 | 0.395 |
| Documented trauma | 17 (17.9%) | 9 (13.2%) | 6 (11.8%) | 0.559 | 0.465 |
| Call time | | | | | |
| 0600–1200 | 13 (13.7%) | 16 (23.5%) | 11 (21.6%) | 0.015 | 0.127 |
| 1200–1800 | 33 (34.7%) | 14 (20.6%) | 19 (37.3%) | | |
| 1800–2400 | 20 (21.1%) | 25 (36.8%) | 14 (27.4%) | | |
| 2400–0600 | 29 (30.5%) | 13 (19.1%) | 7 (13.7%) | | |
| Prior visit | 69 (72.6%) | 39 (57.4%) | 26 (51.0%) | 0.062 | 0.015 |

COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease; HTN = hypertension; CHF = congestive heart failure; DM = diabetes mellitus.

remainder of the haloperidol and benzodiazepine cohort. They were not included as their own cohort because the number of patients was so small (27) that any attempted statistical analysis would have been significantly underpowered. During the haloperidol and benzodiazepine period as well as the ketamine period, no agitated patients received only physical restraint.

## Procedure

Patient encounters from the desired time period were searched for restraint or qualifying medication administration. Once a subject was identified as meeting inclusion criteria, a member of the research team reviewed the associated PCR and the hospital EMR. Data were extracted from qualifying records into a secure Redcap (Version 8.0.0) online database.

## Measures

Demographic and environmental data were extracted from each subject's prehospital PCR and the hospital EMR, including age, gender, weight, medical comorbidity, and the nature of the restraints deployed. All documented weights were scale-recorded measurements from the hospital EMR.

If chemical restraint was administered, the dose of each medication was recorded. Additional environmental data were collected, such as documented co-ingestions, time of day of the call, and whether any prehospital staff members were injured, either before or after patient restraint.

Information extracted from the hospital EMR included outcomes data including length of stay for each encounter (interpreted as time of triage to time of disposition), documentation of further chemical or physical restraint, documentation of any

TABLE 2. Outcomes comparison

| Outcome | Ketamine (n = 95) | Haloperidol + Benzodiazepine (n = 68) | Physical restraint only (n = 51) | Ketamine vs. Haloperidol + Benzodiazepine Odds ratio (confidence interval) | Ketamine vs. Physical restraint only Odds ratio (confidence interval) |
|---|---|---|---|---|---|
| Intubation | 11 (11.6%) | 1 (1.5%) | 3 (5.9%) | 8.77 (1.10–69.68) | 2.10 (0.56–7.88) |
| Admission | 22 (23.2%) | 9 (13.2%) | 6 (11.8%) | 1.97 (0.84–4.61) | 2.26 (0.85–6.00) |
| Additional restraint (any type) | 64 (67.4%) | 33 (48.5%) | 25 (49.0%) | 2.19 (1.15–4.15) | 2.15 (1.07–4.31) |
| Additional chemical restraint | 47 (49.5%) | 17 (25.0%) | 18 (35.3%) | 2.94 (1.49–5.80) | 1.80 (0.89–3.62) |
| Staff injury (before or after med given) | 15 (15.8%) | 6 (8.8%) | 5 (9.8%) | 1.94 (0.71–5.28) | 1.73 (0.59–5.06) |
| ED length of stay, h | | | | | |
| Mean | 9.46 | 9.42 | 6.56 | p = 0.857 | p = 0.002 |
| Median | 7.63 | 7.69 | 5.4 | | |
| Range | 0.93, 30 | 1.47, 56.65 | 0.5, 23.57 | | |

ED = emergency department.

employee injury, documentation of and nature of medical/trauma admission and/or intubation, and any other documentation of medical complications experienced by subjects during their ED course.

## Analysis

Descriptive statistics were calculated on all measures for the 3 cohorts. Comparative statistics were performed for the 3 cohorts (physical restraint only, haloperidol/benzodiazepine administration, and ketamine administration) for all outcome measures, including length of stay, need for further chemical or physical restraint, staff injury, need for hospital admission, intubation, employee injury, and other documented complication attributable to the restraint. All statistical computations were completed using R (Version 2.15.1). p Values were obtained using the Wilcoxon rank sum test for continuous variables such as age and weight, and p values for categorical variables were obtained using chi-square testing. The medical center's institutional review board approved this study.

# RESULTS

## Descriptive Statistics

The descriptive characteristics of our 3 cohorts and the associated statistical comparisons are summarized in Table 1. There was no significant difference between the 3 cohorts in terms of gender, weight, or history of trauma. The ketamine cohort was slightly younger than the physical restraint cohort (mean age of 34.2 years vs. 42.7 years) and there were fewer documented comorbidities in the ketamine group compared to the haloperidol/benzodiazepine cohort (13.7% vs. 33.8%). Patients who received ketamine had a higher incidence of cocaine and opioid ingestion compared to the physical restraint cohort (14.7% and 16.8% vs. 0% and 3.9%) but there was no significant difference between the ketamine and haloperidol/benzodiazepine cohorts in this regard. Nineteen subjects had 2 visits and one subject had 3 visits. They were counted separately for each discrete visit in their respective cohort.

## Comparison of Outcomes Related to Prehospital Restraint Techniques

Table 2 describes the measured outcomes for patients in the 3 different restraint groups. It provides direct statistical comparisons for patient- and provider-centered outcomes after ketamine administration versus haloperidol/benzodiazepine administration or physical restraint only. Patients who were administrated ketamine were more likely to be intubated when compared to the haloperidol/benzodiazepine cohort (11.6% vs. 1.5%), which resulted in an odds ratio (OR) of 8.77 (95% confidence interval [CI], 1.10–69.68). It should be noted that the 3 intubations recorded in the physical restraint–only cohort were related to critical organic illness: one subject had a penetrating chest trauma and lost pulses in the field, and 2 were intubated for hypoxia/respiratory distress in the setting of intracranial hemorrhage.

Patients in the ketamine cohort were also more likely to require additional chemical restraint compared to the haloperidol/benzodiazepine cohort (49.5% vs. 25%; OR =2.94, 95% CI, 1.49–5.80). These same patients were also more likely to require additional chemical and/or physical restraint when compared with the haloperidol/benzodiazepine cohort. The patients in the ketamine cohort had longer average lengths of stay in the ED than the physical restraint–only group (9.46 h vs.

Table 3. Characteristics of ketamine-restrained patients

| | Intubated | Not intubated | p Value |
|---|---|---|---|
| | 11 (11.6%) | 84 (88.4%) | |
| Age, years | | | 0.646 |
| Mean | 32.8 | 34.5 | |
| Median | 33 | 32 | |
| Range | 18, 59 | 18, 63 | |
| Gender | | | 0.992 |
| Male | 7 (63.6%) | 49 (58.3%) | |
| Female | 4 (36.4%) | 35 (41.7%) | |
| Weight, kg | | | 0.894 |
| Mean | 80.4 | 82.5 | |
| Median | 77.1 | 79.7 | |
| Range | 54,102 | 50,136 | |
| Dose, mg | | | 0.966 |
| Mean | 291 | 293 | |
| Median | 300 | 300 | |
| Range | 250, 350 | 150, 400 | |
| Dose, mg/kg | | | 0.576 |
| Mean | 3.71 | 3.62 | |
| Median | 3.78 | 3.66 | |
| Range | 2.45, 4.63 | 1.47, 5.97 | |
| Co-ingestions | | | |
| Alcohol | 5 (45.5%) | 32 (38.1%) | 0.887 |
| Cannabis | 0 (0%) | 4 (4.8%) | |
| Cocaine | 2 (18.2%) | 12 (14.3%) | |
| Opioids | 3 (27.3%) | 13 (15.5%) | |
| Other | 1 (9.1%) | 13 (15.5%) | |
| None | 0 (0%) | 20 (23.8%) | |
| Unknown | 3 (27.3%) | 19 (22.6%) | |
| Any documented co-ingestion | 8 (72.7%) | 45 (54.6%) | 0.379 |
| Trauma | 1 (9.1%) | 16 (19.0%) | 0.695 |
| Comorbidities | | | |
| COPD | 0 (0%) | 3 (3.6%) | |
| Asthma | 1 (9.1%) | 9 (10.7%) | |
| CAD | 0 (0%) | 0 (0%) | |
| HTN | 3 (27.3%) | 7 (8.3%) | 0.161 |
| CHF | 0 (0%) | 1 (1.2%) | |
| DM | 0 (0%) | 6 (7.1%) | |
| Other | 0 (0%) | 13 (15.5%) | |
| Time | | | |
| 0600–1200 | 1 (9.1%) | 12 (14.3%) | 0.718 |
| 1200–0800 | 3 (27.3%) | 30 (35.7%) | |
| 1800–2400 | 2 (18.2%) | 18 (21.4%) | |
| 2400–0600 | 5 (45.5%) | 24 (28.6%) | |

COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease; HTN = hypertension; CHF = congestive heart failure; DM = diabetes mellitus.

6.56 h, $p = 0.002$). However, the length of stay was nearly identical in the ketamine and haloperidol/benzodiazepine cohorts (9.46 vs. 9.42 h). Indications for admission in patients from all cohorts requiring admission are described in Supplemental Table S1.

## Outcomes After Prehospital Ketamine Administration

The characteristics of patients who were administered ketamine are described in Table 3 and broken down by those who were intubated (11) and those who were not (84). There were no significant differences in the average age, gender, weight, dose, co-ingestion, documentation of trauma, comorbidities, or time of presentation between those who were intubated and those who were not. However, there did seem to be a trend for intubated patients to have a documented co-ingestion and to present during the 2400–0600 time period compared to patients who were not intubated (72.7% vs. 54.6% and 45.5% vs. 28.6%, respectively), though neither of these differences reached statistical significance. In the ketamine cohort, 6 of 11 (54.5%) intubations after

TABLE 4. Indication for intubation

| Indication | Ketamine (n = 11) | Haloperidol/benzodiazepine (n = 1) | Physical only (n = 3) |
|---|---|---|---|
| Hypoxia/respiratory distress | 2 | 0 | 2 |
| Refractory agitation | 6 | 1 | 0 |
| Airway protection | 3 | 0 | 1 |

ketamine administration were performed under the supervision of one particular ED provider, whereas the remaining 5 intubations were under the supervision of 5 other providers, a difference that was statistically significant ($p < 0.01$).

Indications for intubation for the 11 of 95 (11.6%) patients who were intubated after ketamine administration are further described in Table 4 and are compared to intubation indications in the other cohorts. Of the patients who received ketamine, 7 of 11 (63.6%) received additional chemical restraint in the ED prior to being intubated, including 5 of 6 patients with refractory agitation, 1 of 2 with hypoxia/respiratory distress, and 1 of 3 requiring airway protection. The single patient intubated from the haloperidol/benzodiazepine group for refractory agitation received additional ED chemical restraint prior to intubation. No patients received additional ketamine in the emergency department. As previously noted, all 3 intubations in the physical restraint–only cohort were precipitated by critical organic illness.

Within the 95 recorded ketamine administrations, there were also 7 other physiologic complications documented in the EMR. For the intubated patients, these included 2 instances of hypersalivation and one case of hypersalivation combined with laryngospasm. For patients who were not intubated, complications included 2 emergence reactions, one incidence of hypersalivation, and one incidence of laryngospasm.

# DISCUSSION

## Complications of Prehospital Ketamine Administration

Our study results are notably different from prior literature in that we report a significantly lower intubation rate (11.6%) than in any previously published study (8–10, 12, 13). One major difference in our protocol is that the average weight-based dose of ketamine was 3.68 mg/kg, whereas prior studies, which had higher intubation rates, averaged between 4 and 5.26 mg/kg. (8–10, 12, 13). It is possible that the lower weight-based dosing contributed significantly to our lower reported intubation rate and should be considered as a possible management tactic to lower intubation rates universally. It is also possible that the "optimal" ketamine dose, which would ideally minimize both the intubation rate and the need for additional rescue sedation, lies between our 3.68 mg/kg average dose and the doses of closer to 5 mg/kg used in previous studies.

The literature has reported several different demographic characteristics associated with the risk of intubation after ketamine administration, including co-ingestion (8), male gender (9), overnight arrival (9), and being seen by specific providers (9, 10), but there is no universal agreement about these risk factors (8–10). Our study did find that a disproportionate number of intubations after ketamine administration were performed under the supervision of one particular ED provider. There are multiple possible explanations for this phenomenon. The provider in question does work predominately overnight shifts in the section of the emergency department that receives the highest acuity patients. It is possible that the threshold to intubate in a high-acuity, low-resource environment is lower than normal because of the risks of caring for a patient with a "precarious" airway in such a setting. It is also possible that some providers are disproportionally uncomfortable with the disassociated patient, who can present with a disconcerting clinical picture. This may be especially true for the relatively undifferentiated patient transported from the prehospital setting, because these patients often arrive with little collateral information. The presence of occult trauma, co-ingestion, and other infectious or metabolic contributors to their altered state is often unknown and may contribute to a provider's level of concern. A study by Hopper et al. (16) examining ketamine use in the emergency department for agitation demonstrated a 0% intubation rate, perhaps indicating that when providers have more control over external factors contributing to a patient's clinical status, they are more comfortable with disassociation.

We also noted a trend, albeit one not reaching statistical significance, toward patients who received ketamine having a higher chance of getting intubated if they had any documented co-ingestion and/or if they arrived during the time period of

2400–0600. No other single demographic characteristic was found to increase the risk of intubation.

These trends speak to the possibility that provider preference, comfort level with the disassociated patient, knowledge of the side effect profile of ketamine, and allocation of available resources for close monitoring may play critical roles in the decision to intubate in this patient population.

## Comparison of Outcomes

Another notable result from our data set is that patients who received ketamine in the field were more likely to require additional ED restraint compared to the haloperidol/benzodiazepine cohort. This may be due to the shorter half-life of ketamine (2.5 h) (14) when compared with haloperidol (21–24 h) (17) and lorazepam (14 h) (18). It is also worth noting that in our study the ketamine cohort had nearly identical ED lengths of stay and admission rates when compared to the haloperidol/benzodiazepine group, so there is no advantage to initial use of ketamine from a disposition standpoint. Patients administered ketamine had a higher rate of documentation of staff injury in the PCR/EMR, although we feel that this outcome is not uniformly documented and therefore may not be entirely accurate (and the CI is not statistically significant for this parameter). It is possible that certain paramedics/staff were more cognizant of documenting injury in the record while they were justifying the use of a new medication (ketamine) in their documentation. Additionally, we had no way of elucidating whether these staff injuries occurred before or after sedation administration.

In this study, at the dosing range used in local protocols, the prehospital use of ketamine did not show any superiority in subjects' ED outcomes compared to haloperidol and benzodiazepine. It did demonstrate the disadvantage of a higher intubation rate in the ED. Nevertheless, it is clear that ketamine has a faster time to effect (11) in the field, an advantage we should not discount. Due to the retrospective model of this study, the level of agitation and the time to adequate sedation in the field were not measured, so we cannot exclude a prehospital benefit. The risk of complications from ExDS increases with length of time (18) and therefore improving agitation as soon as possible is likely protective. Certainly the longer that prehospital providers are tasked with subduing a violent patient, the higher the risk is for injury. The safety of prehospital providers and patients in the prehospital setting is paramount and should be considered a principal concern of medical directors when weighing the risks and benefits of different types of chemical sedation. To this end, ketamine may be considered a temporizing medication, with its speedy onset serving to facilitate safe and timely transportation, but it may not always be the medication of choice to treat agitation.

Overall, it should be considered that there might not be a single "perfect" ketamine dose or a universally optimal sedative option. Ultimately, there are still relatively few data available regarding the dosing range of ketamine for prehospital sedation, and it has yet to be determined whether a more optimal dosing scheme may be developed.

## Limitations

The relatively small sample size and the retrospective chart review model are major limitations of this study. We were not able to include 7 subjects who received ketamine because they were transported to a local community hospital instead of the study site. This study was conducted at a single medical center and therefore local practice patterns, resource limitations, and provider preference may have impacted the intubation rate.

The degree of patient agitation and combativeness was not measured and therefore there is no reliable means of determining whether there is a correlation between the initial severity of agitation and clinical outcomes. The need for physical and/or chemical restraint was at the discretion of the providers based on their comfort level with their safety and that of the patient during transportation and in the emergency department.

Another major limitation of this study is that during the ketamine period, haloperidol and benzodiazepines remained available as standing orders to the EMS providers and there were 27 instances where haloperidol and benzodiazepine were administered instead of ketamine. This may have introduced bias because a certain population was excluded from ketamine administration, likely for a variety of reasons, including EMS provider preference and comfort level with ketamine and patient demographics considered undesirable for ketamine administration such as advanced age, known comorbidity, or preexisting abnormal vital signs. It also introduces the possibility that more agitated patients were being administered ketamine whereas less agitated patients were still being administered haloperidol and benzodiazepine. There is no way to definitively prove or disprove this possibility, because no objective measure of the level of agitation is available. Even if the subjects given haloperidol and benzodiazepine during the ketamine administration period were described and demographically similar to the patients administered ketamine, as the pre-ketamine haloperidol and benzodiazepine cohort is, there is no way to adequately compare level of agitation

between these groups. There are some pieces of collateral information in our results, such as the higher level of staff injury in the ketamine cohort and increased incidence of documented ingestion of an illicit substance ( compared to the physical restraint cohort) that suggest that the patients administered ketamine may have been more agitated as a population. However, it is unlikely that the population as a whole at the study site became globally more agitated at same time that ketamine was introduced as a standing order; therefore, we can postulate that the pre-ketamine haloperidol/benzodiazepine group is similar in overall level of agitation to the ketamine cohort. The increase in documented substance ingestion in the ketamine cohort compared to the physical restraint cohort may also be impacted by the fact that patients who were administered prehospital sedation were more likely to undergo laboratory drug screening and/or more comprehensive documentation of suspected ingestions.

Finally, though we strived to document instances of employee injury as an outcome, they were rarely documented and when they were, it was difficult to determine whether the injury occurred before or after administration of restraint.

## Further Research and Conclusions

The intubation rate we saw in our patient population was lower than reported previously by other authors, but it is higher than is desirable. The decision to intubate is a highly subjective decision. The need to "protect" the airway, although long invoked as a reason to intubate, is imprecise and hard to quantify. This is demonstrated in our study, because one ED provider had an outsized number of intubations, potentially skewing our results.

Additional research will be required to fully investigate the safety profile of ketamine use and to establish parameters so that it can be administered in such a way as to maximize therapeutic effect and minimize complications. It remains to be seen whether ketamine will ultimately prove to be the "ideal" prehospital sedative for combative and belligerent patients or whether there are certain patient populations that respond more favorably to different sedation methods. Certainly, physical restraint in isolation is not always a viable option. Antipsychotics, alone or mixed with benzodiazepines, or benzodiazepines alone are less than ideal given the length of time they take to achieve adequate sedation in an environment when speedy, effective sedation is necessary. Their slow onset of action and unpredictable results do not serve either the patient or treating paramedic well. Further prospective studies are needed to elucidate what patient factors may portend a better course with ketamine versus the antipsychotic/benzodiazepine combination or whether an alternative to ketamine with a similarly short time to adequate sedation may be an acceptable substitute.

We believe that there are 2 pathways forward from here, one prehospital and one in the emergency department. For prehospital providers, it appears to be increasingly certain that dose *does* matter with ketamine. The statewide protocols at the study site specify a dose of 4 mg/kg intramuscularly. This dose may be optimal, because higher doses seem to be associated with higher rates of intubation and complications (8–11). We also speculate that there may be a subset of patients who should *not* be given ketamine in the prehospital setting, but if there is, our data set does not clearly delineate this population, because no distinct group stands out as doing more poorly when administered ketamine.

In the ED, greater regularization and familiarization with dissociated patients, as well as a standardized management toolset for refractory agitation, may lead to a lower frequency of intubations. The well-being of both providers and patients is paramount in the prehospital setting and the safe transportation of agitated, combative patients is a major challenge. Given that physical restraint alone is often not adequate and in itself poses risks to the patient, the employment of chemical restraint remains a necessity.

## References

1. 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. DOI: 10.1016/j.ajem.2014.05.023.
2. 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.
3. Abdon-Beckman D. An awkward position: restraints and sudden death. JEMS. 1997;22(3): 88–90, 92, 94.
4. Baldwin S, Hall C, Bennell C, Blaskovits B, Lawrence C. Distinguishing features of Excited Delirium Syndrome in non-fatal use of force encounters. J Forensic Leg Med. 2016;(41):21–7. doi: 10.1016/j.jflm.2016.03.006.
5. Grant JR, Southall PE, Mealey J, Scott SR, Fowler DR. Excited delirium deaths in custody: past and present. Am J Forensic Med Pathol. 2009;30(1):1–5. doi: 10.1097/PAF.0b013e31818738a0.
6. Vilke DeBard ML, Chan TC, Ho JD, Dawes DM, Hall C, Curtis MD, Costello MW, Mash DC, Coffman SR, McMullen MJ, et al. Excited delirium syndrome (ExDS): defining based on a review of the literature. J Emerg Med. 2012;43(5):897–905. doi: 10.1016/j.jemermed.2011. 02.017.
7. American College of Emergency Physicians. Chemical Restraint in the ED. ACEP Now. Retrieved 2 June 2018 from http://www.acepnow.com/article/chemical-restraint-ed./
8. Burnett A, Peterson B, Stellpflug S, Engebretsen K, Glasrud K, Mark J, Frascone R. The association between ketamine

given for prehospital chemical restraint with intubation and hospital admission. Am J Emerg Med. 2015; 33(1):76–79. doi: 10.1016/j.ajem.2014.10.016.
9. Olives TD, Nystrom PC, Cole JB, Dodd KW, Ho JD. Intubation of profoundly agitated patients treated with prehospital ketamine. Prehosp Disaster Med. 2016;31(6):593–602. Doi: 10.1017/S1049023X16000819
10. Cole JB, Klein LR, Nystrom PC, Moore JC, Driver BE, Fryza BJ, Harrington J, Ho JD. A prospective study of ketamine as primary therapy for prehospital profound agitation. Am J Emer Med. 2017; S0735-6757 (17):30820–3. doi: 10.1016/j.ajem.2017
11. Cole JB, Moore JC, Nystrom PC, Orozco BS, Stellpflug SJ Kornas RL, Fryza BJ, Steinberg LW, O'Brien-Lambert A, Bache-Wiig P, et al. A prospective study of ketamine versus haloperidol for severe prehospital agitation. Clin Toxicol. 2016;54(7):556–62. doi: 10.1080/15563650.2016.1177652.
12. Scheppke KA, Braghiroli J, Shalaby M, Chait R. Prehospital use of IM ketamine for sedation of violent and agitated patients. West J Emerg Med. 2014;15(7):736–41. doi: 10.5811/westjem.2014.9.23229.
13. 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):110–5. DOI: 10.3109/10903127.2014.942478.
14. Ketamine: Drug Information. UpToDate. Retrieved June 1, 2018, from https://www.uptodate.com/contents/ketamine-drug-information.
15. Isenberg, DL and D Jacobs. 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): 491–5. doi: 10.1017/S1049023X15004999.
16. Hopper AB, Vilke GM, Castillo EM, Campilla A, Davie T, Wilson MP. Ketamine use for acute agitation in the emergency department. J Emerg Med. 2015; 48(6):712–9. doi: 10.1016/j.jemermed.2015.02.019.
17. Haloperidol: Drug Information. UpToDate. Retrieved April 1, 2018, from https://www.uptodate.com/contents/haloperidol-drug-information.
18. Lorazepam: Drug Information. UpToDate. Retrieved April 1, 2018, from https://www.uptodate.com/contents/lorazepam-drug-information.