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# Prehospital sedation with ketamine vs. midazolam: Repeat sedation, intubation, and hospital outcomes

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## 1. Introduction

Emergency medical service (EMS) providers often encounter acutely agitated patients who can pose serious threats to themselves, bystanders, and EMS, Fire, and Law Enforcement personnel [1]. Severe, acute, undifferentiated agitation can be a symptom of drug ingestion or underlying medical or psychiatric disorders, and not all agitated patients respond similarly to chemical sedation [2]. Conventionally, paramedics treat agitated patients in the prehospital settings with benzodiazepines to calm the patient sufficiently to complete medical assessment and care. Adverse effects from benzodiazepines including respiratory depression, hypotension, and the need for advanced airway management leave agencies seeking alternative solutions [3].

Within the past decade, ketamine has slowly gained popularity as an alternative to benzodiazepines, but the current literature on use of prehospital ketamine is sparse. The most recent prehospital ketamine literature review identified only 10 studies evaluating ketamine used for agitated adults [4]. The lack of evidence supporting ketamine has stimulated debate among EMS medical directors and administrators on the efficacy, appropriate dosing, and safety profile of the medication. Additionally, few studies comparing ketamine to the more traditional benzodiazepines.

The benefits of ketamine include easy storage, transportation, and administration by a variety of routes, including intramuscular (IM). Studies have demonstrated its efficacy in adequately sedating agitated patients [5], [6] and relatively safety [7], [8]. Ketamine also takes effect quickly, which is advantageous in combative or violent patients [9]. However, ketamine can also cause hypersalivation, emergence reaction, and hypoxia or hypoventilation leading to advanced airway management.

Literature evaluating the relative efficacy and safety of ketamine is limited. Intubations after prehospital sedation, if performed, are often completed in an emergency department, making determination of a true incidence difficult [4]. Additionally, current literature on ketamine use incudes a variety of dosing routes and amounts, making the determination of the ideal dose difficult [4]. Limited research exists on the need for repeat sedation after ketamine use in the prehospital setting [6], [9]. Finally, no research exists on prehospital use of ketamine and associated hospital outcomes leaving EMS leaders with little data to support or refute their use of this new agent.

This study assesses the efficacy of ketamine vs. midazolam in prehospital sedation of acutely agitated patients, specifically evaluating the need for repeat medical sedation by EMS or emergency department personnel. Secondary analyses compare adverse events between each agent, specifically the need for airway support or intubation, need for physical restraints, length of stay, and change in Glasgow coma scale (GCS) outcomes.

## 2. Methods

We retrospectively reviewed the charts of 163 consecutive patients chemically sedated for acute agitation by paramedics in a large third-service EMS agency and transported to an urban level one trauma center in Indianapolis, Indiana that receives about 100,000 patients per year. This study was approved by the Institutional Review Board (IRB) of Indiana University. All patients who received ketamine or midazolam by paramedics between January 1, 2017 and April 1, 2018 were included. Patients <18 years old and patients not transported to the level one trauma center indicated were excluded. Investigators screened prehospital electronic medical records and further excluded any patients who did not receive midazolam for sedation (i.e. seizures). Within this EMS agency, midazolam is the only benzodiazepine used and ketamine is used solely for sedation. Appendix A outlines the agency's chemical sedation protocol. The decision to use either midazolam or ketamine for sedation was at the sole discretion of the paramedic.

For patients with prehospital records meeting the above criteria, investigators reviewed the EPIC® in-hospital medical records system for demographic information, suspicion of illicit drug use, prehospital sedative dosing details (medicine, dose, time, weight-based dosing), and airway interventions. From prehospital records, investigators collected GCS before and after sedation administration. From both prehospital and in-hospital charts, investigators collected repeat sedation dosing and timing, airway interventions, disposition details, and length of stay data. All additional data points were collected and entered into a standard Microsoft Excel™ spreadsheet by 3 investigators. Data was

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coded, exported, and analyzed using IBM SPSS Statistics 24. Descriptive statistics, chi squared, and Mann-Whitney tests were performed.

## 3. Results

The majority of patients were male, and a significantly larger proportion of patients who received ketamine were male compared to those who received midazolam (78.4% vs. 62.1%, $p = 0.024$). Patient ages ranged from 18 to 67. There was no significant difference in patient race, weight, or insurance status. The majority of sedations were due to reported or suspected illicit drug ingestion ($n = 119$, 73%), and this did not significantly differ between ketamine or midazolam groups (Table 1). However, as all patients were acutely agitated on initial presentation, knowledge of underlying medical comorbidities and medications was limited.

Of the 163 patients included in the study, 97 (59.5%) received ketamine and 66 (40.5%) received midazolam for initial chemical sedation. All ketamine administrations were intramuscular and midazolam administrations were either intramuscular ($n = 32$, 48.5%), intravenous ($n = 24$, 36.4%), or intranasal ($n = 10$, 15.1%), at paramedic discretion. Almost all patients received either 300 mg ketamine or 5 mg midazolam (5 patients received 2.5 mg midazolam and 4 received 150 mg ketamine per protocol due to smaller estimated weight). Average weight-based dose for ketamine was 3.75 mg/kg (95% CI 2.13–5.37 mg/kg).

GCS before and after sedation was only reported for 50 (50%) of patients receiving ketamine and 52 (66%) of patients receiving midazolam. For patients administered ketamine, median GCS was 13 (IQR 11.25–15) prior to administration and 9 (IQR 3.25–11.75) after administration (paired $t$-test, $p < 0.0001$); for patients administered midazolam, median GCS was 14 (IQR 13–15) prior to administration and 12 (IQR 6.5–15) after administration (paired $t$-test, $p < 0.0001$). There was no significant difference between the change in GCS achieved with ketamine (mean 5.0, 95% CI 3.6–6.4) and midazolam (mean 4.5, 95% CI 3.4–5.6) (Mann-Whitney test, $p = 0.4116$) (Fig. 1). Given our sample size, a difference in change of GCS of 3 would have been appreciated with power of 0.87, alpha 0.05.

### 3.1. Primary outcome

A significantly greater proportion of patients received repeat sedative dosing (at any time or within 90 min) after initially receiving ketamine vs. midazolam (Table 2). Patients who received more prompt repeat sedation (within 20 min) did not differ between groups. When only IM administrations were analyzed, no significant differences were appreciated in repeat sedation at any time period (Table 3).

Secondary Outcomes.

There were no significant differences in time to repeat sedation, total sedation doses (by EMS or in the emergency department), use of bag valve mask (BVM) or intubation, use of physical restraints, admission location/level of care, or length of stay in the Emergency Department (ED), hospital, or Intensive Care Unit (ICU). Ketamine was re-dosed more often at 90 min (47.4% vs 27.3%, $p = 0.010$) but not at all timepoints (Table 2).

Only 6 (6.2%) of patient were eventually intubated after initially receiving ketamine, dosed from 3.6 to 4.8 mg/kg. Of the 6, one was found to have a traumatic brain injury and one had severe diabetic ketoacidosis. One patient who was intubated received ketamine initially by EMS, subsequently received 5 doses of lorazepam and a dose of haloperidol in the ED and was intubated 8 h after the initial dose of ketamine. The other 3 (3.1%) were intubated within an hour of ED arrival for altered mental status without further complicating factors or further sedative administration.

Intubation rates were similar in the midazolam group. Of the 66 patients who were initially treated with midazolam, 5 (7.6%) were intubated. One patient was found to have a traumatic intracranial hemorrhage. One received repeat sedation (midazolam) before intubation. The other 3 (4.6%) were intubated within an hour of ED arrival for altered mental status without further complicating factors or further sedative administration.

## 4. Discussion

This retrospective review describes the efficacy and safety of ketamine as compared with midazolam for acutely agitated patients in the prehospital setting. While a retrospective review has inherent limitations, this represents a sound sample of a typical urban EMS population. However, for unclear reasons, a higher proportion of males were initially sedated with ketamine. This could be due to a perceived increased aggressiveness of males and need for what could be perceived as a stronger agent.

The primary outcome was need for repeat sedation. A significantly higher proportion of patients received repeat sedation after initial ketamine administration, but most of the repeat sedation was administered in the emergency department. At 20 min, in the prehospital setting, the proportion of patients requiring repeat sedation was not significantly different between the two groups. Since most urban EMS transports are <20 min, it seems reasonable to conclude that EMS providers may not appreciate a need for repeat sedation within this time frame, whereas subsequent hospital staff may re-sedate a patient after further evaluation. When the route of administration was limited to only intramuscular injection, there was no difference in repeat sedation, suggesting some changes in the strength and duration of effect could be route dependent in these patients. This study assessed patients transported to only one county emergency department, and the sedation practiced of physicians in that emergency department may differ from others.

With our sample size, the study would be adequately powered to show a difference between the two cohorts of a change in GCS of 3 or more. It is certainly possible that a type II error was made or that there is a real difference between the two cohorts, leading to a moderate clinical difference. Future prospective studies should be powered adequately to detect a small clinical difference between the two cohorts.

No significant differences in the use of positive pressure ventilation (PPV) or intubation were found, and rates of intubation were relatively low when compared to prior studies. At the hospital studied, patients chemically sedated by EMS are taken to a “high acuity” area, where EM physicians routinely care for critically ill patients and often chemically sedate violent and agitated patients. This may be one reason intubation rates in this study (6.2%) are lower than many of those reported in earlier studies. Those physicians accustomed to regularly treating patients sedated with ketamine or midazolam may be less likely to intubate patients for altered mental status.

**Table 1**
The two groups were comparable in terms of age, race, insurance, weight, and suspicion of illicit drug use ($p < 0.05$) but differed in proportion male gender ($p = 0.024$).

| | Ketamine ($n = 97$) | Midazolam ($n = 66$) |
|---|---|---|
| Mean age in years | 33.8 | 36.1 |
| Male gender | 76 (78.4%) | 41 (62.1%) |
| Race | | |
| White | 46 (47.4%) | 32 (48.5%) |
| African American | 49 (50.5%) | 29 (43.9%) |
| Other | 2 (2.1%) | 5 (7.6%) |
| Insurance | | |
| Self-pay | 24 (24.7%) | 14 (21.2%) |
| Medicaid/Medicare | 42 (43.3%) | 35 (53%) |
| Commercial | 2 (2.1%) | 4 (6.1%) |
| Unknown | 29 (29.9%) | 13 (19.7%) |
| Mean weight in kilograms | 82.1 | 79.1 |
| Suspicion of illicit drugs | 72 (74.2%) | 47 (71.2%) |

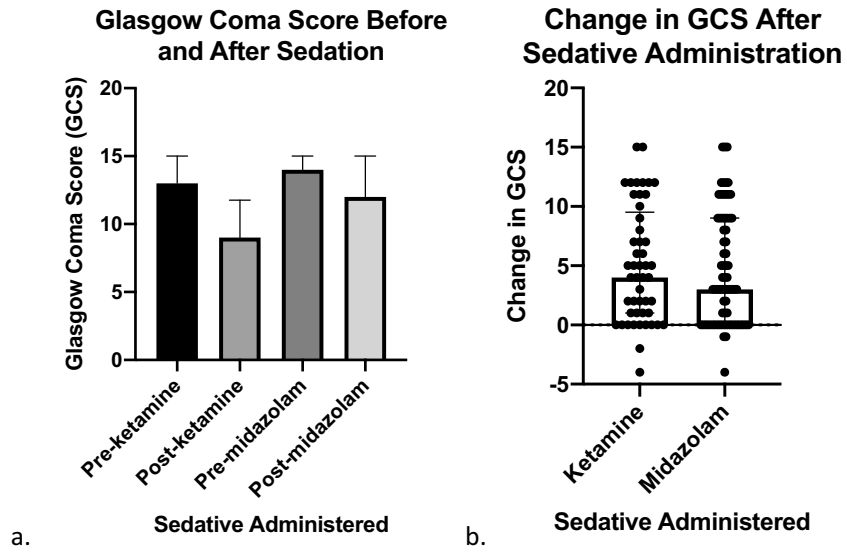


**Fig. 1.** a. For both ketamine and midazolam, there was a significant change in GCS after administration of the sedative ($p < 0.0001$), b. but there was no difference in the change in GCS appreciated by the respective sedatives ($p = 0.4116$).

Six patients were intubated after initially receiving ketamine. Further analysis revealed one patient with an intracranial hemorrhage in each cohort, which may have confounded analysis of the sedation used. Another patient in the ketamine cohort received 6 more doses of sedatives before intubation, suggesting a limited impact of prehospital ketamine on the decision to ultimately intubate. In each group, there were a similar number of patients intubated in the ED for altered mental status after receiving prehospital sedation. Those intubations may be the consequence of sedating medication, in which case the numbers were comparable. Alternatively, the intubations could have resulted from natural progression of the underlying medical pathology, with minimal impact from the prehospital sedative used.

It should be noted that use of ketamine for the acutely agitated patient had recently been introduced into EMS protocols (within 2 years of the study's start date), so paramedics may have been less familiar with ketamine than midazolam. This may have led some paramedics to select midazolam in favor of ketamine. We did not attempt to assess reasons behind paramedic selection of one agent over the other in this study.

A prospective randomized study of ketamine for prehospital sedation would help clarify the optimal dose and route of delivery. However, this study offers reassuring data to support the safety and efficacy of ketamine versus versed. Ketamine remains an important and safe option for prehospital sedation of acutely agitated patients.

**Table 2**
Patients administered ketamine required repeat sedation more often within 90 min and at all times. Otherwise, there were similar outcomes between patients administered ketamine and midazolam. (* Italics indicates statistically significant p-value).

| | Ketamine (n = 97) | Midazolam (n = 66) | Chi-squared *p*-value* |
|---|---|---|---|
| Repeat sedation (any route) | | | |
| Within 20 min | 6 (6.2%) | 7 (10.6%) | 0.306 |
| Within 90 min | 46 (47.4%) | 18 (27.3%) | *0.010* |
| All times | 59 (60.8%) | 26 (39.4%) | *0.007* |
| Time to repeat sedation | 88.8 | 77.2 | 0.658 |
| Total sedation doses | 2.5 | 2.1 | 0.084 |
| Airway interventions | | | |
| PPV | 7 (7.2%) | 3 (4.5%) | 0.741 |
| Intubation | 6 (6.2%) | 5 (7.6%) | 0.758 |
| Physical restraints used | 15 (16.7%) | 10 (16.4%) | 0.965 |
| Disposition | | | |
| Discharged | 70 (72.2%) | 50 (75.8%) | 0.434 |
| Ward/step down/psych | 20 (20.6%) | 9 (13.6%) | |
| Intensive care | 7 (7.2%) | 7 (10.6%) | |
| Length of stay (mean hours) | | | |
| Emergency Department | 9.7 | 9.4 | 0.821 |
| Hospital | 22.0 | 34.3 | 0.336 |
| Intensive Care Unit | 5.8 | 10.9 | 0.366 |

## CRediT authorship contribution statement

**Dustin Holland:** Data curation, Conceptualization, Writing - original draft. **Nancy Glober:** Software, Supervision, Methodology, Writing - review & editing. **Shawn Christopher:** Data curation. **Evan Zahn:** Data curation, Software. **Thomas Lardaro:** Writing - review & editing, Conceptualization. **Dan O'Donnell:** Supervision, Conceptualization, Writing - review & editing.

**Table 3**
When evaluating only sedation given via IM route, requirement for repeat sedation was comparable between ketamine and midazolam

| Repeat sedation | Ketamine (n = 97) | Midazolam (n = 66) | Chi-squared p-value |
|---|---|---|---|
| Within 20 min | 6 (6.2%) | 4 (12.5%) | 0.212 |
| Within 90 min | 46 (47.4%) | 13 (40.6%) | 0.503 |
| Any time | 59 (60.8%) | 17 (53.1%) | 0.443 |

**Appendix A. Indianapolis EMS protocol for chemical restraint**

## Chemical Restraint

Chemical restraint is to be used only where the patient can be adequately and repeatedly monitored by EMT-P providers. It is to be reserved for patients who cannot otherwise be restrained or restrained only at the risk of significant harm to the patient, law enforcement, or EMS providers or if provider has concern for excited delirium. Once applied, patients should be isolated and placed in an ALS ambulance as soon as possible. All patients who are administered midazolam or ketamine are required to be monitored with waveform $EtCO_2$ for adequate ventilation. All patients will be transported to closest appropriate facility for further evaluation.

### ALS

A. Consider other causes of combative or irrational behavior, including but not limited to hypoxia and hypoglycemia.

B. Indications for chemical restraint include

1. Evidence of excited delirium such as drug usage, severe agitation, violent behavior, aggressiveness, hyperthermia, surprising physical strength, lack of response to pain such as Tasers™
2. Violent, agitated patient who cannot be otherwise restrained or restrained only at the risk of significant harm to the patient, law enforcement, or EMS provider

C. Administer ONE of the following:

1. Midazolam IV, IM, or via intra-nasal spray
    a. If patient > 50kg, administer 5 mg IV, IM or IN (2.5 mg in each nostril)
    b. If patient < 50kg, administer 2.5 mg IV, IM, or IN
    c. Consider lower dose if patient is elderly (> 65) or has serious comorbid medical conditions

2. Ketamine IM for patients 12 years of age or older. Preferred medication for patients with suspected excited delirium.
    a. If patient estimated > 50kg, administer 300 mg IM to lateral thigh or deltoid.
    b. If patient estimated < 50kg, administer 150 mg IM to lateral thigh or deltoid
    c. Use with caution in patients with history of coronary artery disease. If there is concern for an acute ischemic event
    d. Larngyospasm is a rare, but serious adverse effect of ketamine administration. If patient develops stridor, apnea, or sudden loss of $ETCO_2$ after administration, suspect laryngospasm.
        i. Apply airway maneuvers, such as jaw thrust or chin lift. Consider oral or nasal airway.
        ii. Assist with BVM at 100% $O_2$ to apply positive pressure.
        iii. If these methods prove to be inadequate and patient is not being ventilated, follow advanced airway protocols with the modification that only a single attempt to visualize the vocal cords should be made with direct laryngoscopy. If vocal cords can be seen and are open, then attempt to intubate with ET tube. If vocal cords are closed/spasming, DO NOT attempt to pass anything through vocal cords and proceed to cricothyrotomy.
        iv. DO NOT administer any further ketamine.

D. Patient should be isolated and placed in an ALS ambulance as soon as possible and all patients will be transported to the nearest appropriate facility for further evaluation and released to law enforcement thereafter.

E. After sedation is achieved

1. Treat any immediate life threatening injuries.

2. Airway, mental status, and vital signs (including **pulse oximetry, waveform $ETCO_2$, and heart rhythm**) must be examined and documented every 5 minutes.
    a. All patients that receive midazolam or ketamine are required to be placed on nasal waveform capnography

3. Monitor for signs of hypoventilation such as decreased respiratory rate or increase in $ETCO_2$
    a. Provide passive oxygenation via nasal cannula or nonrebreather
    b. Attempt verbal and/or physical stimulation
    c. If severe, apply BVM, and move onto advanced airway options per protocol if continued inadequate ventilation

4. Establish IV, initiate IVF therapy

5. Obtain blood glucose level

6. Keep patient in an upright position and allow for hyperventilation.

F. If adequate sedation is not achieved with one of the above options, contact medical control for requests for additional medication or other orders.

1. If medical control recommends additional doses of midazolam or ketamine, either in isolation or in combination, advanced airway preparation should be made, as there is an increased risk for respiratory depression.

G. If patient subsequently has a cardiac arrest, follow ALS protocol for cardiac arrest, but consider early administration of sodium bicarbonate 100mEq IV push if patient initially presented with severe agitation or concerns for excited delirium.

H. If chemical restraint is used, a copy of the run record must be made available to the Medical Director through the CQI Coordinator within 24 hours.

**If chemical restraint is used, a copy of the run record must be made available to the Medical Director through the CQI Coordinator within 24 hours**

(*continued*).

## References


[1] Maguire BJ, Smith S. Injuries and fatalities among emergency medical technicians and paramedics in the United States. Prehosp Disaster Med. 2013;28(4):376–82 Epub 2013/05/11 https://doi.org/10.1017/S1049023X13003555. [PubMed PMID: 23659321].

[2] Pajonk FG, Schmitt P, Biedler A, Richter JC, Meyer W, Luiz T, et al. Psychiatric emergencies in prehospital emergency medical systems: a prospective comparison of two urban settings. Gen Hosp Psychiatry. 2008;30(4):360–6 Epub 2008/07/01 https://doi.org/10.1016/j.genhosppsych.2008.03.005. [PubMed PMID: 18585541].

[3] 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):491–5 Epub 2015/09/02 https://doi.org/10.1017/S1049023X15004999. [PubMed PMID: 26323511].

[4] Linder LM, Ross CA, Weant KA. Ketamine for the acute management of excited delirium and agitation in the prehospital setting. Pharmacotherapy. 2018;38(1):139–51 Epub 2017/11/15 https://doi.org/10.1002/phar.2060. [PubMed PMID: 29136301].

[5] 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):553–9 Epub 2012/07/20 https://doi.org/10.3109/10903127.2012.695434. [PubMed PMID: 22809253].

[6] 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 Epub 2014/08/26 https://doi.org/10.3109/10903127.2014.942478. [PubMed PMID: 25153713].

[7] Burnett AM, Peterson BK, Stellpflug SJ, Engebretsen KM, Glasrud KJ, Marks J, et al. The association between ketamine given for prehospital chemical restraint with intubation and hospital admission. Am J Emerg Med. 2015;33(1):76–9 Epub 2014/12/03 https://doi.org/10.1016/j.ajem.2014.10.016. [PubMed PMID: 25455046].

[8] Scheppke KA, Braghiroli J, Shalaby M, Chait R. Prehospital use of i.m. ketamine for sedation of violent and agitated patients. West J Emerg Med. 2014;15(7):736–41 Epub 2014/12/11 https://doi.org/10.5811/westjem.2014.9.23229. [PubMed PMID: 25493111; PubMed Central PMCID: PMCPMC4251212].

[9] Cole JB, Moore JC, Nystrom PC, Orozco BS, Stellpflug SJ, Kornas RL, et al. A prospective study of ketamine versus haloperidol for severe prehospital agitation. Clin Toxicol (Phila). 2016;54(7):556–62 Epub 2016/04/23 https://doi.org/10.1080/15563650.2016.1177652. [PubMed PMID: 27102743].