A Comparison of Ketamine to Midazolam for the Management of Acute Behavioral Disturbance in the Out-of-Hospital Setting

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Study objective: Acute behavioral disturbance is characterized by altered mental status and psychomotor agitation. Pharmacological sedation may be required, risking potential respiratory compromise. We compared the need for emergent airway support following administration of midazolam or ketamine to treat acute behavioral disturbance in the out-of-hospital setting.

Methods: In this retrospective cohort study of patients with acute behavioral disturbance in an urban emergency medical service system between 2017 and 2021, we compared the likelihood of out-of-hospital advanced airway management following administration of midazolam or ketamine. Advanced airway management was defined as out-of-hospital endotracheal intubation or supraglottic airway insertion.

Results: Among 376 eligible patients, the median age was 35, and 78% were men. The most common etiologies of acute behavioral disturbance were substance use (51%), trauma (18%), and presumed postictal agitation (11%). In all, 162 patients (43%) initially received midazolam and 214 (57%) ketamine. The frequency of advanced airway management was similar between these respective groups (12% [n=19] versus 11% [n=24], difference 0.5%, 95% CI −6.0% to 7.0%). Adjusted for potential confounders, the odds of receiving advanced airway management did not differ between midazolam and ketamine (aOR 1.02, 95% CI 0.44 to 2.38), and no differences were observed in emergency department intubation rates (14% in midazolam recipients, 11% for ketamine) or overall mortality (2% in midazolam recipients, 1% for ketamine).

Conclusion: In this cohort study of patients with acute behavioral disturbance, emergent airway support and other outcomes did not differ following out-of-hospital treatment with midazolam or ketamine. [Ann Emerg Med. 2024;■:1-10.]

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INTRODUCTION

Background

Acute behavioral disturbance is a term used to describe a spectrum of behaviors characterized by altered mental status and psychomotor agitation, associated with an underlying pathology. Acute behavioral disturbance can have many etiologies, including drug intoxication, mental health crisis, hypoglycemia, postictal state, or traumatic brain injury. The clinical presentation remains similar: psychomotor agitation and disturbed consciousness.[1] Physical restraint of combative patients as a standalone measure can place these patients at increased risk of sudden death, whereas their agitation may delay, compromise, or prevent appropriate medical evaluation and emergency care and risk physical harm to care providers.[2]

Importance

Best practice management of patients with acute behavioral disturbance is uncertain. Although initial management emphasizes verbal de-escalation, a subset of patients may require medication treatment for agitation to permit safe medical evaluation, treatment, and transport to hospital.[3] The optimal agent and dosage to achieve rapid tranquility remains unknown. Considerable variation in practice exists, with antipsychotics, benzodiazepines and ketamine all described for this condition, in varying doses and routes of administration.[1] Adverse effects are associated with each of these agents (eg, respiratory depression, airway compromise, hypo- or hypertension, and QTc prolongation) that can unpredictably exacerbate the patient's underlying medical condition. Ketamine and benzodiazepines are the most commonly used agents in the

Editor's Capsule Summary

What is already known on this topic

Respiratory compromise can result from pharmacological tranquilization.

What question this study addressed

When treating out-of-hospital acute behavioral disturbance with midazolam versus ketamine, is there a difference in the need for emergent airway support?

What this study adds to our knowledge

In this observational comparison of 376 adults receiving protocol-driven doses of either midazolam (1 to 5 mg intravenous/intramuscular as needed every 2 to 5 minutes) or ketamine (5 mg/kg up to 500 mg intramuscular), later rates of intubation or supraglottic airway insertion did not differ, nor did secondary outcomes.

How this is relevant to clinical practice

Based on these nonexperimental observations, no safety advantage exists between typical protocolized doses of midazolam or ketamine for acute emergency medical service behavioral management.

out-of-hospital setting in the United States.[4] Few studies have directly compared the potential benefits and risks between such agents or reported limited inhospital follow-up.

Goals of the Investigation

The primary goal of this study was to compare the use of emergent out-of-hospital airway support after the administration of ketamine or midazolam for out-of-hospital acute behavioral disturbance management. Secondary goals evaluated out-of-hospital and emergency department (ED) complications and outcomes for patients who received either drug during the out-of-hospital management of this condition.

MATERIALS AND METHODS

Study Design and Setting

We performed a retrospective cohort study comparing the outcomes and complications associated with out-of-hospital use of either midazolam or ketamine as pharmacotherapy for patients with acute behavioral disturbance over a 4-year study period (February 6, 2017 to February 9, 2021). The relevant institutional review boards (IRBs) granted approval for this research under minimal risk criteria (STUDY00013223). We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to guide and document our approach (see Appendix E1, available at http://www.annemergmed.com).[5]

Setting

The study was conducted in an urban population of 740,000 people served by a single emergency medical service (EMS) agency. Since 2015, intramuscular or intravenous midazolam has been the benzodiazepine used for postintubation sedation, anxiolysis, and seizure termination, as well as a treatment option for acute behavioral disturbance when given after consultation with a physician. For sedation of an agitated patient, the guideline recommended a midazolam dose of 1 to 5 mg intramuscular or intravenous, repeated as needed every 2 to 5 minutes. In 2015, ketamine was incorporated into the local EMS formulary as an induction agent for rapid sequence intubation and as an alternative to midazolam for acute behavioral disturbance. The protocol initially called for a 300 mg intramuscular dose for adults, before being changed in 2016 to a 5 mg/kg intramuscular dose, up to a maximum of 500 mg. Paramedics had a standing order for intramuscular ketamine administration when a risk to patient or provider safety did not offer sufficient time for consultation with a physician prior to treatment. Intravenous administration for treatment of acute behavioral disturbance required prior approval from an online medical consultation physician.

Selection of Participants

Potential subjects were identified by querying all out-of-hospital electronic health records over the 4-year study period by first screening for records containing the words "ketamine," "versed," or "midazolam" in the list of medications administered or in the free text narrative. Among the records that contained at least one of these terms, a secondary search scanned the free text notes for specific terminology associated with acute behavioral disturbance. We selected terms a priori to include any one of the following: aggressive, aggressively, agitated, agitation, belligerent, combative, danger, delirium, erratic, exds, fighting, handcuffed, handcuffs, naked, restraints, screaming, spitting, spit sock, threatening, uncooperative, or unwilling. Patients of any age were considered eligible for inclusion. Figure 1 illustrates a flow diagram of study population identification.

To ensure only the population of interest was identified, the EMS free text notes that contained one or more of the secondary search terms, for example, aggressive, were de-

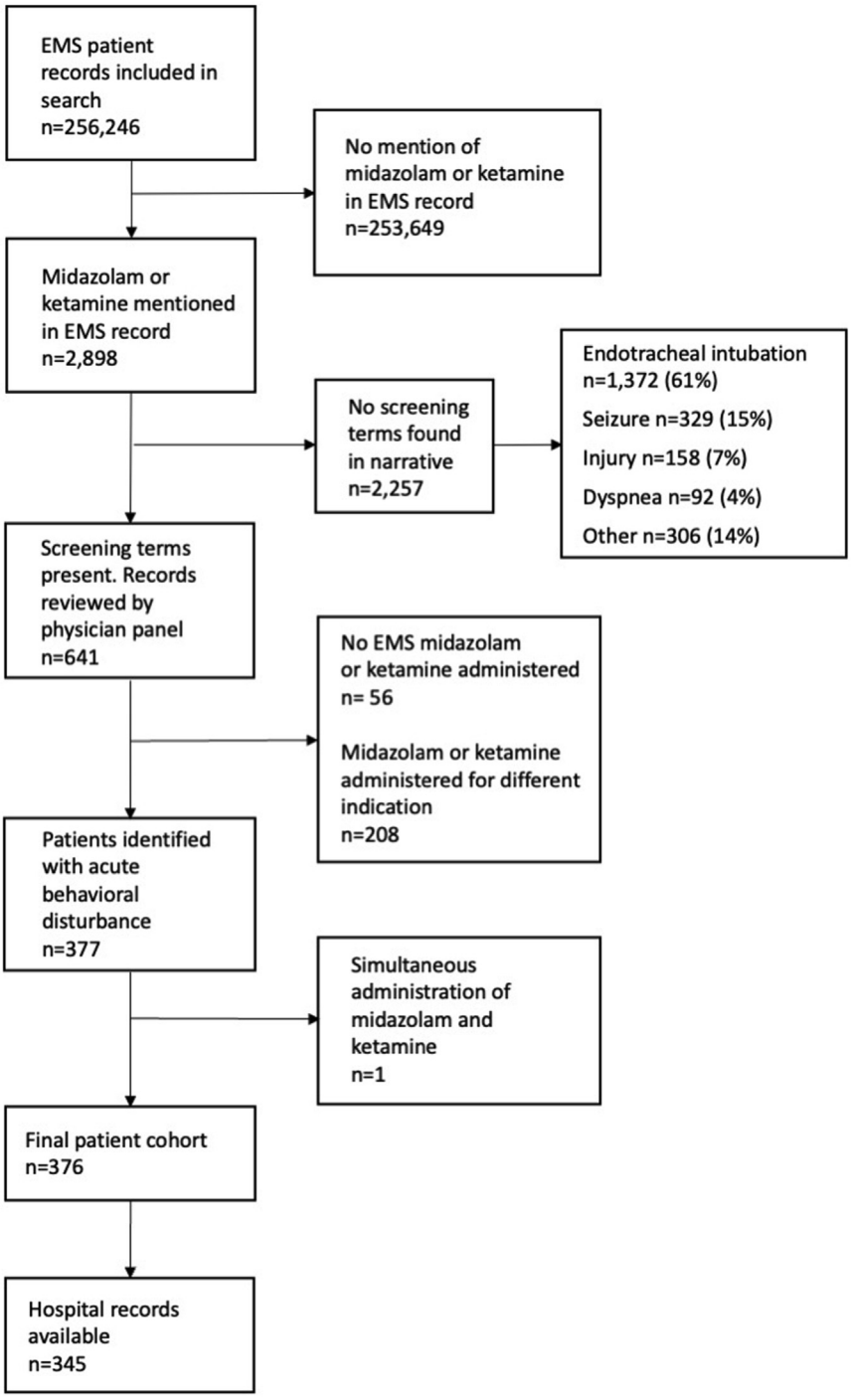

Figure 1. Process to identify cohort of interest. Among the 2,257 records when no screening terms were found in the EMS narrative, 61% documented tracheal intubation with ketamine or midazolam. The remaining records were divided into categories based on the EMS impression (seizure, injury, dyspnea, or other).

identified of study medication name and dosage. Then the notes were independently reviewed by 2 of 4 physicians (MMu, SRS, AMM, and RN) who knew the study hypothesis to determine if midazolam or ketamine was given to manage acute behavioral disturbance or for a different indication such as seizure termination, anxiolysis, analgesia, or planned rapid sequence intubation (Kappa 0.65, standard error [SE] 0.04). Acute behavioral disturbance was operationally defined as a mentally altered patient, deemed by scene providers to require pharmacological therapy to safely evaluate, treat, or transport. Initial discrepancies between the 2 physician

reviewers were resolved by independent assessment by 2 additional physicians, with resolution by 4-physician consensus.

Measurements

Study information was collected from both out-of-hospital and hospital electronic health records as well as a prospectively collected out-of-hospital advanced airway management registry using a standardized collection form. After vetted selection of cases eligible for study, a trained reviewer (MCM), who was aware of the study hypothesis, abstracted patient demographics, dose, route, and timing of all medications administered, vital signs recorded during assessment and transport, suspected cause of acute behavioral disturbance, advanced airway management details in the out-of-hospital and ED settings, complications related to advanced airway management, laboratory test results and hospital disposition. The trained reviewer determined one primary cause and zero to multiple secondary etiologies of acute behavioral disturbance.

To assess interrater reliability in data abstraction, a random sample of 50 records from the study population, 25 with and 25 without out-of-hospital advanced airway management, were abstracted a second time by an independent reviewer (MRS) who was aware of the study hypothesis. The agreement between the 2 reviews was high across all key variable comparisons, Kappa ranged from 0.80 to 0.92 for key data elements (Table E1, available at http://www.annemergmed.com). In cases of disagreement between the first and second abstraction of key variables of interest (eg sedation medications, airway management techniques, and outcomes) a third abstractor (SRS) acted as a tiebreaker.

Outcomes

The primary outcome was emergent out-of-hospital advanced airway management after medication treatment for acute behavioral disturbance, defined by attempted tracheal intubation or use of a supraglottic airway.

Secondary outcomes of interest were the use of advanced airway management in the ED, documentation of medication-associated hypoxemia (oxygen saturation <90%), receipt of additional sedation, cardiac arrest at any point following study drug administration, disposition from the ED, hospital admission to an intensive care unit (ICU), duration of mechanical ventilation, length of hospital stay, and final hospital discharge disposition. Outcomes were stratified by the first field medication given, either midazolam or ketamine, regardless of administration of additional doses of the first medication or crossover to the other medication.

Analysis

Outcomes were determined according to initial treatment with midazolam versus ketamine. For select variables, we calculated the difference in 2 proportions and the 95% CI for that difference. To account for potential confounding, we compared the likelihood of the outcome of EMS advanced airway management according to midazolam or ketamine using multivariable logistic regression. We considered age, sex, cause of acute behavioral disturbance (substance use or mental health crisis versus all other), and route of first administration (intravenous or intramuscular) for the regression models, along with the exposure of interest, midazolam (0) or ketamine (1). We used age and sex as they are standard covariates. We used primary cause of acute behavioral disturbance and route of first administration as they are important clinical variables that could be associated with the exposure of interest and the outcome. In exploratory analyses using a similar logistic regression model, we a priori evaluated the subgroup of patients who received their initial treatment through the intramuscular route as these patients likely reflect the group that was more severely agitated, and hence more difficult to manage, than those permitting intravenous access. Analyses were conducted using Stata (version 16.0; StataCorp, College Station, TX).

RESULTS

Characteristics of Study Participants

Of 2,897 patient records with a mention of the study drugs, 585 met criteria suggestive of possible acute behavioral disturbance and were screened by blinded physician review. Most of the patients, having none of the keywords indicative of acute behavioral disturbance, received ketamine or midazolam as part of tracheal intubation (Figure 1). Physician review determined that 377 patients met criteria for having pharmacologically treated acute behavioral disturbance. The final cohort included 376 patients after excluding one patient who received both study drugs at the same time (Figure 1). Our IRB approval limited the review of hospital records to 345 patients who were transported to 3 adult hospitals and one pediatric hospital within its jurisdiction. Although their EMS phase of care was included in the primary analysis, 31 patients transported to noncovered hospitals were lost to follow-up. The missingness of certain data elements is shown in Table E2 (available at http://www.annemergmed.com).

Midazolam was the initial treatment for 162 (43%) patients, and ketamine was initially administered to 214 (57%) (Table 1). Compared to those treated with midazolam, recipients of ketamine were younger and less frequently women.

The most common primary etiologies of acute behavioral disturbance were presumed substance use, trauma, and suspected postictal agitation. Ketamine was used more often when the primary cause was substance use, whereas midazolam was used more often for postictal agitation and other medical etiologies (Table 1). Patients treated initially with ketamine had higher blood pressure and pulse rates. Initial Glasgow Coma Scale (GCS) score and oxygen saturation did not differ between treatment groups. The time from 911 call to hospital arrival was similar in both groups. More patients were lost to hospital follow-up following midazolam administration than ketamine. Consistent with paramedic impressions, urine drug screens more often indicated the presence of illicit drugs in those treated with ketamine. Laboratory measures of kidney function and creatine kinase did not differ according to midazolam versus ketamine (Table E3, available at http://www.annemergmed.com).

Primary Outcome

A total of 43 patients (11%) with acute behavioral disturbance received out-of-hospital advanced airway interventions, a proportion that did not differ according to initial treatment with midazolam or ketamine (Table 2). When adjusted for age, sex, substance use or mental health cause and intramuscular route of first administration, the odds ratio of receiving an out-of-hospital advanced airway intervention after use of ketamine compared to midazolam as reference did not differ (odds ratio 1.02, 95% CI 0.44 to 2.38; Table E4, available at http://www.annemergmed.com). Analysis by subgroups did not reveal any significant differences (Figure 2 and Tables E5 to E7, available at http://www.annemergmed.com).

Of the 37 patients who received both midazolam and ketamine in the EMS setting, 13 (35%) received out-of-hospital airway intervention. Twelve of the 13 patients received the second agent (ie, midazolam after ketamine, or ketamine after midazolam) for sedation during advanced airway placement. The sole remaining patient received midazolam after ketamine, followed by a transient period of bag mask ventilation, and was not intubated in the EMS or ED settings (Table E8, available at http://www.annemergmed.com).

Secondary Outcomes

Among the 345 patients transported to a hospital having regulatory approval for information access, the frequency of new ED airway management did not differ between midazolam and ketamine cohorts (Table 2 and Figure E1, available at http://www.annemergmed.com). The initial out-of-hospital drug administered was not associated with subsequent receipt of supplementary sedation in the ED.

Patients who initially received out-of-hospital midazolam were less likely to be discharged from the ED than those who initially received ketamine (Table 2). ICU admission was primarily associated with the need for mechanical ventilatory support and did not differ by study drug. The total duration of ventilatory support and the length of hospitalization did not differ between groups (Table 2).

Nine patients received cardiopulmonary resuscitation (CPR) in the EMS setting (Table E8). In total, 5 patients died, including 3 who initially received midazolam and 2 who initially received ketamine.

One patient who received 500 mg ketamine intramuscularly for agitation following recent methamphetamine use became pulseless 2 minutes later. Return of spontaneous circulation (ROSC) was noted after 18 minutes of resuscitation. The patient died in the ICU from diabetic ketoacidosis exacerbated by methamphetamine use. The second patient became altered after illicit substance use and received 10 mg midazolam intramuscularly. Cardiac arrest occurred 15 minutes later. ROSC was not achieved, and the patient was pronounced dead in the ED from hyperthermia from drug intoxication. The third patient was found agitated and received 500 mg ketamine intramuscularly. Cardiac arrest developed 4 minutes later. ROSC was achieved after 11 minutes, but the patient rearrested on route to the ED. Toxicology screen was positive for methamphetamine. The patient died from multiorgan failure. The fourth patient was found to be combative with a blood glucose level of 36 mg/dL. After 25 g intravenous dextrose, the patient remained combative and was given 2.5 mg midazolam intravenously. After receiving an additional dose of midazolam intravenously, the patient developed cardiac arrest. ROSC was initially achieved, but death occurred in the ICU from hypoglycemia and aspiration pneumonia. The fifth patient was a pedestrian struck by a truck who was agitated with a GCS score of 10. The patient received 5 mg midazolam intramuscularly followed about 5 minutes later by etomidate, rocuronium, and endotracheal intubation. Vital signs remained stable during the out-of-hospital phase. The patient died 3 days later from severe traumatic brain injury.

Five patients who received out-of-hospital CPR were discharged home after hospitalization. One patient had cardiogenic pulmonary edema and a peri-intubation cardiac

Table 1. Patient characteristics and disposition from scene.

Category	Midazolam First	Ketamine First	Difference	95% CI
All patients (n, % of row)	162 (43%)	214 (57%)		
Patient demographics				
Age (y)*	42 (19)	36 (12)	6	2.8 to 9.2
Women	48 (30%)	35 (16%)	13.3%	4.7% to 21.9%
Out-of-hospital narrative review				
Drug use reported	71 (44%)	113 (52%)	−9.0%	−19.1% to 1.2%
Combativeness reported	144 (89%)	200 (93%)	−4.6%	−10.4% to 1.3%
Restraints reported	81 (50%)	172 (80%)	−30.4%	−39.7% to −21.0%
Primary cause of ABD				
Substance use	53 (33%)	139 (64%)	−32.2%	−41.9% to −22.6%
Trauma	30 (19%)	37 (17%)	1.2%	−6.6% to 9.1%
Postictal agitation	26 (16%)	15 (7%)	9.0%	2.4% to 15.6%
Mental health crisis	10 (6%)	16 (7%)	−1.3%	−6.4% to 3.8%
Glycemic emergency	14 (9%)	2 (1%)	7.7%	3.2% to 12.2%
Cardiovascular	12 (7%)	2 (1%)	6.5%	2.2% to 10.7%
Dyspnea	9 (6%)	3 (1%)	4.2%	0.3% to 8.0%
Other medical	8 (5%)	0 (0%)	4.9%	1.6% to 8.3%
First EMS vital signs				
Glasgow Coma Scale score*	11.3 (4.4)	12.1 (3.9)	−0.8	−1.7 to 0.1
Systolic BP (mm Hg)*	146.1 (37.2)	156.6 (32.5)	−10.5	−18.3 to −2.7
Diastolic BP (mm Hg)*	84.9 (21.4)	96.4 (20.7)	−11.6	−17.3 to −5.8
Respiratory rate (breaths/min)*	21.5 (9.1)	22.0 (9.1)	−0.5	−2.4 to 1.4
SpO_2 (%)*	96.3 (4.6)	96.9 (3.6)	−0.6	−1.6 to 0.3
Pulse rate (beats/min)*	112 (32)	122.9 (26)	−10.9	−17 to −4.7
$ETCO_2$ (mm Hg)*	36.9 (12.0)	39.9 (11.7)	−3	−7.1 to 1
Total out-of-hospital time (minutes)*	47.6 (16.9)	47.5 (19.2)	0.1	−3.6 to 3.8
Out-of-hospital sedative use				
Midazolam (number treated)	162 (100%)	30 (14%)	86.0%	81.3% to 90.6%
Total dose (mg)†	5 (2.5 to 5)	5 (5 to 5)		
Ketamine (number treated)	7 (4%)	214 (100%)	−95.7%	−98.8% to −92.5%
Total dose (mg)†	500 (200 to 500)	500 (500 to 500)		
EMS disposition				
Transported to ED covered by IRB approval	138 (85%)	207 (97%)	−11.5%	−17.5% to −5.6%
Transported to ED outside IRB approval	22 (14%)	7 (3%)	10.3%	4.5% to 16.1%
Left alive on scene	1 (1%)	0 (0%)	0.6%	−0.6% to 1.8%
Unknown disposition	1 (1%)	0 (0%)	0.6%	−0.6% to 1.8%
Patients with available hospital records	138 (85%)	207 (97%)	−11.5%	−17.5% to −5.6%
ED toxicology panel results‡				
Ethanol > 0.08 mg/dL	21 (15%)	21 (10%)	5.1%	−2.2% to 12.3%
Amphetamines	26 (19%)	89 (43%)	−24.2%	−33.5% to −14.8%
Barbiturates	0 (0%)	0 (0%)	0.0%	0.0% to 0.0%
Benzodiazepines	74 (54%)	38 (18%)	35.3%	25.4% to 45.1%
Cocaine	12 (9%)	29 (14%)	−5.3%	−12.0% to 1.4%

Table 1. Continued.

Category	Midazolam First	Ketamine First	Difference	95% CI
Opiates	14 (10%)	34 (16%)	−6.3%	−13.4% to 0.9%
Phencyclidine (PCP)	0 (0%)	5 (2%)	−2.4%	−4.5% to −0.3%
Cannabis	33 (24%)	70 (33%)	−9.9%	−19.5% to −0.3%
Toxicology panel not done	53 (38%)	51 (25%)	13.8%	3.8% to 23.8%

ABD, Acute behavioral disturbance; *ED*, emergency department; *EMS*, emergency medical service. Unless otherwise noted, each row shows patient count and percentage of patients in that column.
*Mean (standard deviation).
†Median (interquartile range).
‡Limited to 345 patients with available hospital records.

arrest following midazolam. Three patients had agitation treated with midazolam following out-of-hospital ventricular fibrillation cardiac arrest. A fifth patient received 5 mg midazolam intramuscularly for agitation from severe asthma who developed cardiac arrest, achieved ROSC 5 minutes later, and was admitted to the ICU.

LIMITATIONS

This investigation is retrospective and observational, thus vulnerable to biases and confounding. The choice of who received treatment was not prospectively determined, but rather at provider discretion. Selection of midazolam or ketamine presents the potential for confounding by indication. Midazolam was used more frequently among those who had a suspected underlying medical cause of acute behavioral disturbance, as compared to ketamine, which was administered more frequently to those with a presentation related to suspected substance use. Residual confounding may influence the current results. For example, we were not able to incorporate information about underlying comorbidities.

The study involved a single EMS system in an urban environment where the paramedics have substantial experience in advanced airway management, a circumstance that may limit generalizability. We evaluated the association between specific medication use and emergent out-of-hospital advanced airway support, appreciating there are other important outcomes that may also be influenced by medication selection. Moreover, the study had limited power to detect outcome differences between midazolam and ketamine. The 95% CIs ranging from -6.0% to 7.0% for the primary endpoint may not exclude a clinically important difference.

Care of patients experiencing acute behavioral disturbance is not standardized but rather determined by the likely cause. Consequently, not all patients receive laboratory exams, urine toxicology, or blood alcohol levels, perhaps introducing a bias toward those where positive results were expected. We included advanced airway management for any indication in the ED, so its need may not be reflective of sedation received in the field, but rather of other emerging indications. Finally, pediatric representation in this study was small.

DISCUSSION

Acute behavioral disturbance is the manifestation of an underlying, potentially life-threatening, process of medical or psychological cause, which requires prompt intervention to ensure patient and provider safety.[6] The optimal pharmacological agent to achieve rapid tranquility is unknown, but both midazolam and ketamine are used for this indication. These medications are known to have adverse effects on ventilation. In this retrospective cohort study, the frequency of out-of-hospital emergent airway support after medication delivery for acute behavioral disturbance did not differ between initial treatment with midazolam or ketamine. Moreover, we did not observe a difference in the need for additional airway support in the ED, need for additional sedation after arrival in hospital, or length of stay.

The reported association between ketamine for initial management of acute behavioral disturbance and subsequent tracheal intubation varies substantially. Some studies have recorded rates as high as 57% to 63%, whereas others have reported rates as low as 6.2%.[7-9] A meta-analysis examining both the out-of-hospital and ED settings found an invasive airway rate of 20% (95% CI 11% to 33%) among patients who received ketamine.[10] We observed a proportion of patients in both initial treatment groups who were agitated as a result of severe traumatic injury or critical illness and needed airway protection for reasons other than adverse drug effects.

The current study population was heterogenous, including all-cause acute behavioral disturbance. Some studies examining ketamine for the management of acute

Table 2. Patient outcomes.

Outcome	Midazolam First	Ketamine First	Difference	95% CI
All Patients (N, % of Row)	162 (43%)	214 (57%)		
Primary outcome				
Highest out-of-hospital advanced airway				
Tracheal tube	19 (12%)	24 (11%)	0.5%	−6.0% to 7.0%
Supraglottic airway	0 (0%)	0 (0%)		
Bag mask ventilation only	6 (4%)	2 (1%)	2.8%	−0.4% to 6.0%
Patient maintained airway	137 (85%)	188 (88%)	−3.3%	−10.4% to 3.8%
Secondary outcomes				
Out-of-hospital cardiac arrest				
Arrest before sedative medication	3 (2%)	0 (0%)	1.9%	−0.2% to 3.9%
Arrest after sedative medication	3 (2%)	3 (1%)	0.4%	−2.2% to 3.1%
Out-of-hospital death	0 (0%)	0 (0%)		
Patients with available hospital records (n, % of all patients)	138 (85%)	207 (97%)	−11.5%	−17.5% to −5.6%
Airway at end of ED care*				
EMS-placed tracheal tube	15 (12%)	24 (12%)	−0.7%	−7.5% to 6.1%
EMS-placed tracheal tube with extubation in ED	2 (1%)	0 (0%)	1.4%	−0.5% to 3.4%
ED placed tracheal tube	19 (14%)	23 (11%)	2.7%	−4.5% to 9.8%
Supraglottic airway	0 (0%)	0 (0%)		
Bag mask ventilation only	0 (0%)	1 (0%)	−0.5%	−1.4% to 0.5%
Patient maintained airway	102 (74%)	159 (76%)	−2.9%	−12.2% to 6.4%
ED cardiac arrest*	1 (1%)	1 (0%)	0.2%	−1.5% to 1.9%
Additional sedative medications in ED*				
Midazolam	29 (21%)	39 (19%)	2.2%	−6.5% to 10.8%
Ketamine	8 (6%)	10 (5%)	1.0%	−3.9% to 5.8%
Lorazepam	34 (25%)	55 (26%)	−1.9%	−11.3% to 7.4%
Haloperidol	13 (9%)	22 (11%)	−1.2%	−7.6% to 5.2%
Propofol	20 (15%)	23 (11%)	3.4%	−3.9% to 10.6%
RSI medications†	17 (12%)	24 (12%)	0.7%	−6.3% to 7.7%
Opioids	32 (23%)	35 (17%)	6.3%	−2.4% to 15.0%
No additional sedative medications	57 (41%)	85 (41%)	0.2%	−10.4% to 10.8%
Disposition from ED*				
Admitted to intensive care	46 (33%)	55 (27%)	6.8%	−3.1% to 16.7%
Admitted to floor or another hospital	32 (23%)	38 (18%)	4.8%	−4.0% to 13.6%
Discharged	59 (43%)	114 (55%)	−12.3%	−23.0% to −1.6%
Died in ED	1 (1%)	0 (0%)	0.7%	−0.7% to 2.1%
Duration of mechanical ventilation (in days, median and IQR)	0.95 (0.41-1.90)	0.66 (0.41-1.35)		
Duration of hospital stay (in days, median and IQR)	0.95 (0.28-4.07)	0.73 (0.30-2.13)		
Final disposition*				
Discharged to independent living	118 (86%)	185 (89%)	−3.9%	−11.1% to 3.4%
Discharged to long term care facility	12 (9%)	16 (8%)	1.0%	−5.0% to 6.9%
Transferred to another hospital	5 (4%)	4 (2%)	1.7%	−1.9% to 5.3%
Died in hospital	3 (2%)	2 (1%)	1.2%	−1.6% to 4.0%

CPR, Cardiopulmonary resuscitation; *ICU*, intensive care unit; *RSI*, rapid sequence induction.
Unless otherwise noted, each row shows patient count and percentage of patients in that column.
†Limited to the 345 patients with available hospital records.
*RSI drugs = rocuronium, succinylcholine or etomidate.

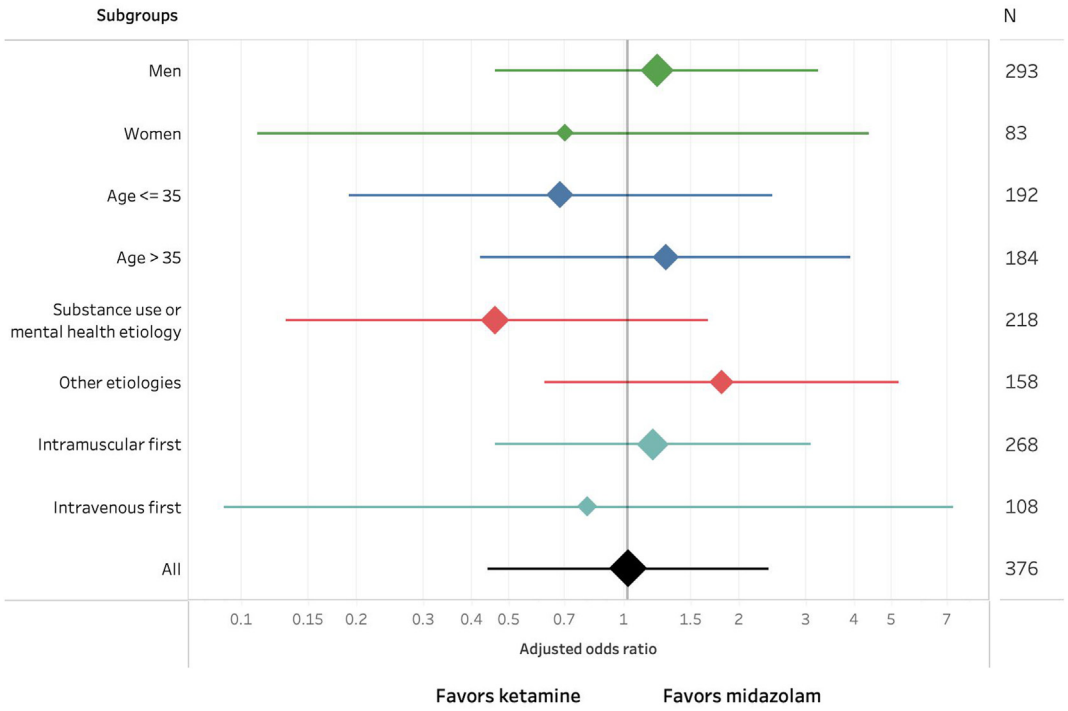

Figure 2. Adjusted odds ratios and 95% confidence intervals are shown for each subgroup in the primary regression analysis.

behavioral disturbance have included only the most common causes: drug use, especially stimulant use, and mental health disorders.[11-13] In our study, any patient who received sedation for agitation management was eligible for inclusion. Ketamine administration was highest among patients who subsequently tested positive for amphetamines and cocaine on urine drug screen. There are several plausible reasons for this difference. This subgroup may represent the most agitated and combative patients in this cohort. They were also predominantly younger men, for whom the perceived threat of violence and physical harm may be more than that of frailer patients. The clinical presentation, collateral history, and presence of drug paraphernalia would all suggest the likelihood of polysubstance misuse, and EMS providers may be concerned about the respiratory depressant effects of midazolam interacting with drugs used by the patient. Ketamine can be administered through the intramuscular route with a rapid onset of action, and perhaps has a more rapid onset than a combination of benzodiazepines and haloperidol, attributes that are desirable in this instance.[7,14,15]

The optimal dose of ketamine or midazolam to induce sedation for acute behavioral disturbance remains unknown. Regarding ketamine, varying protocols have ascribed doses of 4 mg/kg to 5 mg/kg intramuscularly in the out-of-hospital environment; however, in the ED, some authors have examined dose reductions to 2 mg/kg intramuscularly when being used as a second-line agent or to mitigate drug side effects.[16-19] The efficacy of a 5 mg/kg intramuscular dose has been demonstrated; however, the reported incidence of subsequent tracheal intubation varied widely by clinical settings (57% out-of-hospital versus 0% ED).[2,7,17,20] The protocolized use of intramuscular ketamine, as is the case in our cohort, has previously been shown to result in lower rates of out-of-hospital tracheal intubation; and provider comfort with the use of these medications has likely increased over time, which may explain our relatively lower rate of invasive ventilation compared to some previous studies.[13,21] Finally, initial doses of midazolam vary and likely influence the need for airway support.

Although our results are limited by methodological design, they suggest that ketamine is a reasonable option for acute behavioral disturbance treatment, achieving an airway safety profile that does not significantly differ from midazolam. Future efforts to improve care for acute behavioral disturbance should consider how to best classify, enroll, and compare patients—potentially by cause and acute physiological parameters—while considering details about drug, dose, route, and timing. Although an important goal, prospective randomized trials to study this topic more definitively are challenging, making robust observational assessments a useful contribution to clinical understanding.

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