ORIGINAL RESEARCH

Patient Outcomes Following Ketamine Administration for Acute Agitation with a Decreased Dosing Protocol in the Prehospital Setting

Cassidy Cunningham, MS;[1] Karen Gross, EMT-P;[2] John P. Broach, MD, FACEP;[2] Laurel O'Connor, MD[2]

1. University of New England College of Osteopathic Medicine, Biddeford, Maine USA
2. Department of Emergency Medicine, University of Massachusetts Medical School, Worcester, Massachusetts USA

Correspondence:
Cassidy Cunningham, MS
University of New England College of Osteopathic Medicine
11 Hills Beach Road, Biddeford, Maine 04005 USA
E-mail: cunninghamcassidy0@gmail.com

Conflicts of interest/funding/disclaimer: 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. The views expressed in the submitted article are those of the authors' and not an official position of the institutions.

Keywords: acute agitation; ketamine; paramedic; safety; sedation

Abbreviations:
ED: emergency department
EMR: electronic medical record
EMS: Emergency Medical Services
IM: intramuscular
IV: intravenous
NMDA: N-Methyl-D-Aspartate
PCR: prehospital care reports

Received: October 22, 2020
Revised: December 12, 2020
Accepted: December 20, 2020

doi:10.1017/S1049023X21000236
© The Author(s), 2021. Published by Cambridge University Press on behalf of the World Association for Disaster and Emergency Medicine.

Abstract

Background: Agitated behaviors are frequently encountered in the prehospital setting and require emergent treatment to prevent harm to patients and prehospital personnel. Chemical sedation with ketamine works faster than traditional pharmacologic agents, though it has a higher incidence of adverse events, including intubation. Outcomes following varying initial doses of prehospital intramuscular (IM) ketamine use have been incompletely described.

Objective: To determine whether using a lower dose IM ketamine protocol for agitation is associated with more favorable outcomes.

Methods: This study was a pre-/post-intervention retrospective chart review of prehospital care reports (PCRs). Adult patients who received chemical sedation in the form of IM ketamine for agitated behaviors were included. Patients were divided into two cohorts based on the standard IM ketamine dose of 4mg/kg and the lower IM dose of 3mg/kg with the option for an additional 1mg/kg if required. Primary outcomes included intubation and hospital admission. Secondary outcomes included emergency department (ED) length of stay, additional chemical or physical restraints, assaults on prehospital or ED employees, and documented adverse events.

Results: The standard dose cohort consisted of 211 patients. The lower dose cohort consisted of 81 patients, 17 of whom received supplemental ketamine administration. Demographics did not significantly differ between the cohorts (mean age 35.14 versus 35.65 years; P = .484; and 67.8% versus 65.4% male; P = .89). Lower dose subjects were administered a lower ketamine dose (mean 3.24mg/kg) compared to the standard dose cohort (mean 3.51mg/kg). There was no statistically significant difference between the cohorts in intubation rate (14.2% versus 18.5%; P = .455), ED length of stay (14.31 versus 14.88 hours; P = .118), need for additional restraint and sedation (P = .787), or admission rate (26.1% versus 25.9%; P = .677). In the lower dose cohort, 41.2% (7/17) of patients who received supplemental ketamine doses were intubated, a higher rate than the patients in this cohort who did not receive supplemental ketamine (8/64, 12.5%; P <.01).

Conclusion: Access to effective, fast-acting chemical sedation is paramount for prehospital providers. No significant outcomes differences existed when a lower dose IM ketamine protocol was implemented for prehospital chemical sedation. Patients who received a second dose of ketamine had a significant increase in intubation rate. A lower dose protocol may be considered for an agitation protocol to limit the amount of medication administered to a population of high-risk patients.

Cunningham C, Gross K, Broach JP, O'Connor L. Patient outcomes following ketamine administration for acute agitation with a decreased dosing protocol in the prehospital setting. ***Prehosp Disaster Med.*** **2021;36(3):276–282.**

Introduction

Patients exhibiting agitated behavior are frequently encountered in the prehospital setting. They require emergency treatment to prevent harm to the patient and prehospital providers.[1] Agitated behavior and agitated delirium can also arise from psychiatric, traumatic, and organic causes. These include metabolic/endocrine derangements, drug intoxications, drug

https://doi.org/10.1017/S1049023X21000236 Published online by Cambridge University Press

withdrawal, infections, and encephalopathy.[2] Agitation-related emergencies can include but are not limited to suicide attempt/ideation, ingestions, psychosis, depression, trauma, and acute neurological pathologies.[1] Chemical sedation is an important aspect of the treatment for agitated behaviors as physical restraint in isolation can be dangerous and exacerbate pathologies related to agitation. Complications of physical restraint in isolation have been extensively examined in the prehospital setting. They include asphyxiation, especially in prone positioning, hyperthermia, overdose/substance use, trauma, and sudden death.[3]

Traditional pharmacologic treatment methods for psychiatric emergencies include haloperidol, promethazine, olanzapine, midazolam, lorazepam, and droperidol. Combinations of these agents decrease agitation, but they can take time to work, putting providers at risk. Antipsychotic medications in particular also have significant adverse effect profiles, including extrapyramidal symptoms and acute dystonia.[4] Ketamine, an anesthetic derivative of phencyclidine,[5] is currently commonly favored as a means of chemical sedation. Its use preserves protective airway reflexes, has a rapid onset of action, and minimally increases intracranial pressure. These favorable properties cause ketamine to be used frequently to treat acute agitation in the prehospital and hospital emergency department (ED) settings.[6] Glutamate N-Methyl-D-Aspartate (NMDA) receptor antagonism is thought to attribute to the dissociative, psychedelic, and analgesic properties of ketamine.[5]

Prior studies have compared the use of intramuscular (IM) ketamine to traditional IM haloperidol and IM benzodiazepines for control of acute agitation.[7,8] Time to sedation with ketamine was significantly faster than haloperidol (five minutes versus seventeen minutes). However, complication rates were significantly higher with ketamine administration than haloperidol alone. These included hypersalivation, emergence reaction, vomiting, dystonia, laryngospasm, and akathisia.[7,9,10] Comparison of intubation rates between ketamine and haloperidol use in acute agitation revealed ketamine had a significantly higher intubation rate than haloperidol and a combination of haloperidol and benzodiazepines.[7,8] Patients who received ketamine were also more likely to require additional chemical sedation and restraint compared to patients who received haloperidol and benzodiazepines.[8]

There is some equipoise in the literature regarding whether there is a direct relationship between ketamine dose and subsequent intubation. In one prior study, patients intubated in the ED following ketamine administration received a mean dose of 6.2mg/kg IM, while patients not intubated had a mean dose of 4.9mg/kg IM.[11] In another study, the dose did not appear to matter; 63% of their subjects were intubated after receiving the ketamine, with the median administered dose of 5.25mg/kg for intubated patients and 5.14mg/kg for non-intubated patients.[12] Documented reasons for intubation following prehospital ketamine administration were respiratory depression or cardiac arrest with co-ingestion, trismus and bradycardic arrest, and irregular bradypnea.[12] In other studies examining lower dose protocols, intubation rates ranged from four percent to twelve percent.[8,13]

Rates of respiratory depression and intubation following varying initial doses of IM ketamine use have not been thoroughly examined. Many current protocols give paramedics standing orders for the administration of 4mg/kg IM dose of ketamine to a maximum dose of 400mg for adults in the prehospital setting.[14] The primary aim of this study was to determine if utilizing a lower dose of ketamine (3mg/kg IM, followed by a 1mg/kg IM injection if acute agitation persists) for agitation and agitated delirium leads to lower intubation rates and a more favorable side effect profile than the standard dose of 4mg/kg IM. The secondary goals were to describe whether patients were more likely to receive additional chemical sedation and physical restraints in the ED following utilization of a lower ketamine dose compared to the standard dose, the rate of medical admission in these patients, and the impact on instances of violence towards staff.

Methods

Setting and Participants

This study was conducted at an urban academic medical center. The Emergency Medical Service (EMS) studied was a hospital-based ground ambulance service. Patients over the age of 18 transported by paramedics who received chemical sedation during a 9-1-1 emergency call in the prehospital setting in the form of ketamine for acute agitation or agitated delirium were considered for inclusion in this study. Pregnant patients, patients under the age of 18, and prisoners were excluded from the study. Patients who received ketamine for reasons other than agitation and agitated delirium (for example, analgesia and intubation induction) were excluded from the study. Patients who received a different form of chemical sedation for acute agitation, including lorazepam, haloperidol, midazolam, or other medications utilized for chemical sedation, were excluded. Patients transported by ambulance services other than the hospital-based ambulance or transported to a hospital outside of the institution's system were excluded from the study as their ED course could not be obtained. Approximately 15% of all patients transported in the city of interest were transported to an outside hospital.

Subjects were treated from January 1, 2017 through December 31, 2019. Before May 1, 2019, the protocol in place directed the administration of 4mg/kg IM ketamine for patients over 18 years of age for agitation and agitated delirium and considered a threat to themselves or prehospital providers, based on estimated patient weight. After May 1, 2019, the protocol was adjusted and directed paramedics to give an initial dose of 3mg/kg IM ketamine based on estimated weight for agitation and agitated delirium. If adequate sedation was not achieved, up to 1mg/kg IM ketamine based on estimated weight could be administered as the second dose.

Physical restraints utilized by EMS providers included handcuffs from police on scene and soft restraints for wrists and ankles in the ambulance during transport. All subjects were administered IM ketamine for agitation or agitated delirium.

In total, 711 charts were identified for ketamine administration; 418 charts were excluded where ketamine was administered for intubation or pain management, or the patient's alias specified in the prehospital chart could not be located in the hospital electronic medical record (EMR) and no ED course could be obtained. One patient who received ketamine was under 18 years of age and was excluded from the study. The study included a total of 292 charts. All charts involving chemical sedation administration were reviewed by a medical director for completion and accuracy within 72 hours to ensure they were an accurate representation of the patient's clinical course and the actions taken by paramedics.

Charts were extracted from two time periods to compare the outcomes of the patients who were under the lower dose protocol for ketamine administration compared to those who received the standard dose protocol. The two cohort groups were designated by querying charts for prehospital use of ketamine, based on the original dosing of 4mg/kg IM injection and the lower dosing of 3mg/kg IM injection. Emergency department course information was derived from hospital EMRs. The cohort before protocol

https://doi.org/10.1017/S1049023X21000236 Published online by Cambridge University Press

change included 211 charts, and the cohort following the protocol change included 81 charts.

Procedure

Prehospital care reports (PCRs) were identified based on ketamine administration during the study period. Once charts were identified for inclusion, they were reviewed by a member of the research team. Prehospital care reports were matched with each subjects' hospital EMR, and charts were reviewed for additional clinical information. Data were extracted from PCR and EMR charts meeting inclusion and exclusion criteria and recorded in a secure Redcap database (Version 9.3.0; Vanderbilt University; Nashville, Tennessee USA). This study was approved by the University of Massachusetts Institutional Review Board (Worcester, Massachusetts USA; IRB Docket H00019697).

Measures

Information on each subject's demographics and hospital course was recorded. Prehospital care reports specified indications for medication administration. Additional environmental data were collected and recorded, including medical comorbidities, documented co-ingestions, and the time of day of the call. The following outcomes of interest were recorded and analyzed: prehospital or ED intubation, medical admission from the ED, ED length of stay, additional chemical sedation/physical restraints, assault on prehospital or ED employees, documented adverse effects, and complications experienced during ED course.

Analysis

Descriptive statistics were calculated, and comparative statistics were performed for demographics and outcome data for both cohorts. These outcome data included: mean ketamine dose, ED length of stay, need for additional chemical sedation or physical restraint, comorbidities, co-ingestions, documented prehospital trauma, EMS call times, intubation, and medical/trauma admission to the hospital. All statistical computations were completed using R version 4.2.0 (R Foundation for Statistical Computing; Vienna, Austria). P values were obtained utilizing Chi-square analysis for binary variables and two-tailed T testing for continuous variables.

Results

Descriptive Statistics

Descriptive statistics from both the standard dose cohort and the lower dose cohort are summarized in Table 1. Patient age, gender, or weight did not significantly differ. Documented comorbidities, co-ingestions, documented traumatic injuries, or time of EMS call between the cohorts also did not differ significantly. A significant difference was identified in the mean ketamine dose (mg/kg) administered for patients in the standard dose cohort and lower dose cohort (mean dose of 3.51mg/kg standard dose cohort versus 3.24mg/kg lower dose cohort; P = .03). In the lower dose cohort, patients receiving a second dose of ketamine received an average of 4.33mg/kg compared to those who received a single dose (2.95mg/kg; t = 6.9599; P <.001). This was also significantly increased from the standard dose cohort, who received an average of 3.51mg/kg (t = 4.18; P <.001).

Comparison of Outcomes Related to Dose of Ketamine Administered

Table 2 describes clinical outcomes between cohorts. Lower dose cohort patients did not have a statistically significant lower intubation rate (14.2% standard dose cohort versus 18.5% lower dose cohort; P = .455). Similarly, there was no significant difference in admission rate (medical or trauma) between the cohorts (26.1% standard dose cohort versus 25.9% lower dose cohort; P = .677). Patients were equally likely to receive additional chemical sedation and physical restraint (72.0% standard dose cohort versus 72.8% lower dose cohort; P = .787) and additional chemical sedation in the absence of physical restraint (57.3% standard dose cohort versus 56.8% lower dose cohort; P = .27) in the ED. Indications for intubation for both cohorts are described in Table 3.

In the lower dose cohort, adequate sedation without additional dosing was achieved in 79% (64/81) patients. An additional dose of 1mg/kg IM ketamine following the initial dose of 3mg/kg IM ketamine was administered to 21% (17/81) of patients in the lower dose cohort to achieve adequate sedation. Out of those 17 patients, 10 did not require intubation. An additional three of the 17 patients were intubated in the hospital: two for agitation/delirium and one for agitation/delirium and hypoxia. Paramedics intubated the remaining four patients in the prehospital setting: two for hypoxia/respiratory depression, one for airway protection, and one for refractory agitation/delirium. Seven out of 15 (47%) of the intubations were comprised of patients who received an additional ketamine dose in the lower dose cohort. The lower dose patients who received additional ketamine had a statistically significant increase in the intubation rate compared to the cohort that did not (41% in the group that received supplemental ketamine, 11% in the group that did not; $X^2 = 11.36$; P <.01). There was also a higher intubation rate in the patients who received supplemental doses of ketamine in the lower dose group than in the standard dose group (41.2% versus 14.2% standard dose cohort; OR = 5.60; CL 1.66-18.85; P <.01). The intubation rate of standard dose cohort patients did not significantly differ compared to lower dose cohort patients who did not receive supplemental ketamine (14.2% standard dose versus 12.5% lower dose; P = .73).

The average ED length of stay was not different between the standard and lower dose cohorts (14.31 hours standard dose cohort versus 14.88 hours lower dose cohort; P = .118). A statistically significant increase in staff assaults was seen following protocol change (19.4% documented staff injuries standard dose cohort versus 43.2% lower dose cohort; OR = 3.15; P <.001). The locations of staff injuries are described in Supplemental Material (available online only). Prehospital staff injuries occurred before ketamine administration, while hospital staff injuries occurred after paramedics administered ketamine based on documentation in PCRs and hospital EMR. There was no statistically significant association between employee injury and patient intubation in the lower dose group ($X^2 = 0.08$; P = .78).

Comparison of Adverse Effects Related to Dose of Ketamine Administered

The Supplemental Material describes the adverse effects documented for patients in both cohorts. In the standard dose cohort, 22.3% (n = 47/211) patients had documented adverse reactions, while 21.0% (n = 17/81) patients in the lower dose cohort reported an adverse reaction; the difference between the two cohorts was not statistically significant.

Discussion

Outcomes After Prehospital Ketamine Administration

This study demonstrated intubation rates of 14.2% when patients received an average of 3.51mg/kg of ketamine and 18.5% when patients received an average of 3.24mg/kg of ketamine. This

https://doi.org/10.1017/S1049023X21000236 Published online by Cambridge University Press

	All Subjects (n = 292)	Standard Dose Cohort (n = 211)	Lower Dose Cohort (n = 81)	
	Number (%)	Number (%)	Number (%)	P
Age (years)				
Mean	35.28	35.14	35.65	.484
Median	32	32	31	
Range	18, 86	18, 86	20, 83	
Gender				
Male	196 (67.1)	143 (67.8)	53 (65.4)	
Female	96 (32.9)	68 (32.2)	28 (34.6)	.89
Weight (kg)				
Mean	86.2	85.84	87.13	.56
Median	81.65	81.6	81.65	
Range	50, 204.12	50, 204.12	59, 158.76	
Ketamine Dose (mg/kg)	**3.44**	**3.51**	**3.24**	**.03**
Comorbidities				
COPD	8 (2.7)	7 (3.3)	1 (1.2)	.568
Asthma	25 (8.6)	20 (9.5)	5 (6.2)	.509
CAD	0 (0.0)	0 (0.0)	0 (0.0)	NA
HTN	36 (12.3)	25 (11.9)	11 (13.6)	.827
CHF	2 (0.7)	2 (0.9)	0 (0.0)	NA
DM	21 (7.2)	16 (7.6)	5 (6.2)	.877
Other	68 (23.3)	44 (20.9)	24 (3)	.146
Co-Ingestions				
Alcohol	105 (36)	80 (37.9)	25 (30.9)	.595
Cannabis	33 (11.3)	22 (10.4)	11 (13.6)	.336
Cocaine	59 (20.2)	38 (18.0)	21 (25.9)	.569
Opioids	65 (22.3)	44 (20.9)	21 (25.9)	.172
Other	92 (31.5)	58 (27.5)	34 (42.0)	.426
None	46 (15.8)	35 (16.6)	11 (13.6)	.0231
Unknown	61 (20.9)	49 (23.2)	12 (14.8)	.160
Documented Trauma	62 (21.2)	45 (21.3)	17 (21)	1.00
Call Time				
600-1200	48 (16.4)	31 (14.7)	17 (21.0)	.09
1200-1800	89 (30.5)	68 (32.2)	21 (25.9)	
1800-2400	84 (28.8)	51 (24.2)	33 (40.7)	
2400-600	71 (24.3)	61 (28.9)	10 (12.3)	
Prior Visit	173 (59.5)	123 (58.6)	50 (61.7)	.655

Cunningham © 2021 Prehospital and Disaster Medicine

Table 1. Subject Demographics
Abbreviations: COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; HTN, hypertension; CHF, congestive heart failure; DM, diabetes mellitus.

intubation rate is similar to two recent studies[8,15] with average doses of ketamine 4mg/kg or lower but was significantly lower than several previously published studies[11,12] with average doses of 6.16mg/kg and 5.20mg/kg, respectively.[11,12] Patients who received a supplemental dose of ketamine for sustained agitation had a higher mg/kg dose and a significantly higher intubation rate than patients who received either the initial 4mg/kg or the new protocol dose of up to 3mg/kg IM ketamine. Although this may be dose-related, these differences also raise the possibility that patients who are more agitated (and therefore require additional ketamine) are ultimately more prone to intubation. It is also possible that there is a potentiating effect from the split dosing, although such a phenomenon has not been described in other literature. The etiology of this finding is beyond the scope of this project, but it warrants additional investigation.

While there is not enough evidence to suggest causation between the reduced dose of ketamine and decreased need for intubation, this study contributes to the body of literature that suggests an association between lower dose utilization and lower intubation rates.[7,8,11,12,15] Though the decrease in dosing protocol from 4mg/kg to 3mg/kg yielded a similar intubation rate, there may be another dosing threshold that could be prospectively validated that is associated with a decrease in intubation rate.

https://doi.org/10.1017/S1049023X21000236 Published online by Cambridge University Press

	All Subjects (n = 292)	Standard Dose Cohort (n = 211)	Lower Dose Cohort (n = 81)			
Outcome	**Number (%)**	**Number (%)**	**Number (%)**	**X^2**	**OR (95% CI)**	**P**
Intubation	45(15.4)	30(14.2)	15(18.5)	0.533	1.37 (0.69–2.71)	.46
Admission	76(26)	55(26.1)	21(25.9)	0.178	0.98 (0.66–1.45)	.68
Additional Restraint (any type)	211(72.3)	152(72)	59(72.8)	0.076	1.04 (0.59–1.85)	.79
Additional Chemical Restraint	167(57.2)	121(57.3)	46(56.8)	0.002	0.98 (0.58–1.64)	.27
Staff Injury (before or after med given)	**76(26)**	**41(19.4)**	**35(43.2)**	**15.97**	**3.15 (1.81–5.50)**	**<.05**
Adverse Reactions	64(21.9)	47(22.2)	17(20.9)	0.32	0.93 (0.5–1.73)	.675
ED Length of Stay (hours)				**t**	**Δ (95% CI)**	
Mean	14.47	14.31	14.88	−0.346	0.57 (−3.06–4.20)	.12
Median	10.33	9.83	11.9			
Range	0.32, 110.33	0.32, 110.33	2.9, 53.25			

Cunningham © 2021 Prehospital and Disaster Medicine

Table 2. Outcomes Comparison

Indication	Standard Dose Cohort (n = 30)	Lower Dose Cohort (n = 15)
Hypoxia/Respiratory Distress	10 (34.5)	6 (40.0)
Refractory Agitation	9 (31.0)	5 (33.3)
Airway Protection	9 (31.0)	4 (26.7)
Facilitate Imaging	1 (3.4)	0 (0.0)
Missing	1 (3.4)	0 (0.0)

Cunningham © 2021 Prehospital and Disaster Medicine

Table 3. Indication for Intubation

The precipitation of the "need" for intubation remains controversial. There is potential for a brief period of apnea if intravenous (IV) ketamine is pushed as a quick bolus, with the administration of high doses of ketamine, or when combined with other sedative or analgesic agents; however, this is typically avoided with IM administration.[16,17] Some patients may have consumed other substances before receiving ketamine (a higher proportion than the general population, given the demographics of patients who require chemical sedation). It is also possible that provider discomfort with the mental status of a dissociated patient may result in the decision to initiate invasive ventilation. A lower dose of ketamine results in a shorter dissociation period and has a lesser potentiating effect with other substances. Therefore, it is less likely to induce a clinical presentation concerning for compromised airway.[17]

Ultimately, while the decrease in ketamine dosing protocol did not decrease intubation rates, it did not meaningfully change any other patient outcomes, including the length of stay, rate of adverse events, need for additional sedation and restraint, and need for admission. The lower dose may be equally efficacious in achieving the goal of safely transporting most agitated patients to the ED. However, some patients in the lower dose cohort did receive additional ketamine to facilitate safe transportation to the hospital. Since administering an IM medication to an agitated patient is a high-risk task that may result in staff injury, the risks and benefits of a decreased dosing protocol that may require additional medication administrations to patients should be weighed carefully.

Non-Intubation Adverse Outcomes

Sub-anesthetic ketamine doses lead to dissociation and psychotic symptoms and impair episodic and semantic memory due to NMDA antagonism. Ketamine at anesthetic levels can cause emergent states with hallucinations, nightmares, delirium, and vivid dreams.[16] Salivary hypersecretion can occur after ketamine administration and may lead to higher rates of laryngospasm. Ketamine administration has also been associated with nausea/vomiting and increased severity of nausea reported by patients.[18] Previous studies reported complication rates of around forty-nine percent in patients who received ketamine. Complications included hypersalivation in thirty-eight percent of patients, ten percent with emergence reactions, nine percent with vomiting, and five percent with laryngospasm.[7] This current study had similar outcomes as previous research regarding complication rates of ketamine administration.

A dose-dependent relationship for documented adverse reactions could not be established as this relied on the quality of PCR and electronic medical record documentation in the retrospective chart review. Previous studies described a dose-dependent relationship when ketamine was administered through various methods, including IM, IV, subcutaneous, and oral routes of administration. A dose-dependent relationship has shown dissociative effects, including depersonalization, derealization, and altered time and body perception.[19] As with intubation, the frequency of other adverse outcomes in this study did not change in a statistically significant way when a lower dose protocol was instituted, which suggests that there may be similar safety profiles in a 3mg/kg and 4mg/kg dosing protocol. A lower dose may be considered desirable to decrease the total dosage of psychoactive medications administered.

Prehospital and Hospital Staff Assault

Violence against prehospital and hospital personnel is an important consideration during every patient interaction. Previous studies found

https://doi.org/10.1017/S1049023X21000236 Published online by Cambridge University Press

violence in up to 8.5% of patient encounters, with about one-half of this directed at prehospital providers.[20,21] Previous studies revealed assaults on prehospital providers accounted for 8.0% of occupational fatalities and 2.0% of nonfatal occupational injuries.[21] The higher rate of documented staff assault in this current study is alarming. Patient encounters with ketamine administration before protocol change had a 19.4% rate of reported staff assault, while this rate was 43.2% after the protocol change.

While the higher rate of documented assault may be an indicator that the lower dose of ketamine was ineffective in achieving adequate chemical sedation and ensuring provider safety, this was felt to be less likely by the authors as all other indicators, including the need for additional restraint and sedation, were unchanged between the groups. There was no increase in assaults on staff after ketamine administration in the lower dose cohort. Most documented staff injuries took place in the prehospital setting before ketamine administration.

The reason for the increase in reports of staff assaults could be multifactorial. There may be a desire to "justify" the use of ketamine sedation in the setting of increased scrutiny from the lay public. Reported rates of assaults on EMS providers in the system of interest, independent of ketamine administrations, were notably increased in the past two years, the same period during which this study was conducted. Additionally, a more rigorous electronic reporting model for instances of violence towards providers was implemented into the system's PCR software. The high rate of reported assaults on health care providers highlights the importance of ensuring the availability of safe and effective chemical sedation, especially in the prehospital setting. It also emphasizes the possibility that adding an as-needed second dose to a sedation protocol may increase the risk to prehospital providers.

Limitations

This study was conducted at a single site, which may impact external validity. The lower dose cohort had a relatively small sample size compared to the standard dose cohort. This may have resulted in data that were underpowered to detect some differences between the cohorts. The small sample size could affect the extrapolation to the general population. This study was completed as a pre-/post-intervention retrospective chart review, and information gathered for the study relied on documentation in prehospital PCRs and EMRs. Data were limited by the inability to get an accurate real-time weight for all patients. The degree of patient agitation and combativeness was not documented objectively and could not be factored into outcomes. Time to second dose for the subpopulation of patients who received additional ketamine could not be reported with high fidelity as times for medication administration were estimated by paramedics.

There are multiple future directions for research pertaining to ketamine administration in the prehospital setting. One important focus is a prospective description of the adverse reactions of ketamine administration at different doses and rates of staff injuries with more standardized documentation. More investigation is also needed to create a validated prehospital scale for patient agitation and combativeness, which will allow a more rigorous comparison of the amount of chemical sedation received in relation to the level of agitation and the subsequent risk of complications. Finally, research should be conducted to compare outcomes of various co-ingestions in addition to ketamine administration to determine what impact ingestions have on clinical outcomes when combined with ketamine.

Conclusions

Primary and secondary outcome measures, including intubation rate, hospital admission, ED length of stay, additional chemical sedation/physical restraints, assault on staff, documented adverse effects, and complications experienced during ED course, were successfully evaluated. No significant outcomes differences existed when a lower dose IM ketamine protocol was used for prehospital chemical sedation. Patients requiring supplemental doses of ketamine may have higher rates of intubation. A lower dose protocol may be considered for an agitation protocol to limit the amount of medication administered to a population of high-risk patients. However, the use of a "second dose" protocol does entail some risk to providers. Access to effective, fast-acting chemical sedation is paramount for prehospital providers as they grapple with alarming levels of patient violence. Further research is needed to optimize the dose of ketamine for agitation to minimize complications and maintain provider and patient safety.

Supplementary Materials

To view supplementary material for this article, please visit https://doi.org/10.1017/S1049023X21000236

References

1. Pajonk FG, Schmitt P, Biedler A, et al. Psychiatric emergencies in prehospital emergency medical systems: a prospective comparison of two urban settings. *Gen Hosp Psychiatry.* 2008;30(4):360–366.
2. Gill JR. The syndrome of excited delirium. *Forensic Sci Med Pathol.* 2014;10(2):223–228.
3. Abdon-Beckman D. An awkward position: restraints and sudden death. *JEMS.* 1997;22(3):88.
4. Bak M, Weltens I, Bervoets C, et al. The pharmacological management of agitated and aggressive behavior: a systematic review and meta-analysis. *Eur Psychiatry.* 2019;57:78–100.
5. Wolff K, Winstock AR. Ketamine: from medicine to misuse. *CNS Drugs.* 2006;20(3):199–218.
6. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. *Ann Emerg Med.* 2011;57(5):449–461.
7. Cole JB, Moore JC, Nystrom PC, et al. A prospective study of ketamine versus haloperidol for severe prehospital agitation. *Clin Toxicol (Phila).* 2016;54(7):556–562.
8. O'Connor L, Rebesco M, Robinson C, et al. Outcomes of prehospital chemical sedation with ketamine versus haloperidol and benzodiazepine or physical restraint only. *Prehosp Emerg Care.* 2019;23(2):201–209.
9. Linder LM, Ross CA, Weant KA. Ketamine for the acute management of excited delirium and agitation in the prehospital setting. *Pharmacotherapy.* 2018;38(1):139–151.
10. Mankowitz SL, Regenberg P, Kaldan J, Cole JB. Ketamine for rapid sedation of agitated patients in the prehospital and emergency department settings: a systematic review and proportional meta-analysis. *J Emerg Med.* 2018;55(5):670–681.
11. Burnett AM, Peterson BK, Stellpflug SJ, et al. The association between ketamine given for prehospital chemical restraint with intubation and hospital admission. *Am J Emerg Med.* 2015;33(1):76–79.
12. 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.
13. Scheppke KA, Braghiroli J, Shalaby M, Chait R. Prehospital use of IM ketamine for sedation of violent and agitated patients. *Western J Emerg Med.* 2014;15(7):736–741.
14. Massachusetts Department of Public Health. "2.4 Behavioral Emergencies Adult & Pediatric." In: *Emergency Medical Services Prehospital Statewide Treatment Protocols* (V2019.2). Boston, Massachusetts USA: Massachusetts Department of Public Health Office of Emergency Medical Services; 2019.

https://doi.org/10.1017/S1049023X21000236 Published online by Cambridge University Press

15. Li M, Martinelli AN, Oliver WD, Wilkerson RG. Evaluation of ketamine for excited delirium syndrome in the adult emergency department. *J Emerg Med.* 2019;S0736-4679(19):30802–30809.
16. Gao M, Rejaei D, Liu H. Ketamine use in current clinical practice. *Acta Pharmacol Sin.* 2016;37(7):865–872.
17. Tobias JD, Leder M. Procedural sedation: a review of sedative agents, monitoring, and management of complications. *Saudi J Anaesth.* 2011;5(4):395–410.
18. Song JW, Shim JK, Song Y, Yang SY, Park SJ, Kwak YL. Effect of ketamine as an adjunct to intravenous patient-controlled analgesia, in patients at high risk of postoperative nausea and vomiting undergoing lumbar spinal surgery. *Br J Anaesth.* 2013;111(4):630–635.
19. Loo CK, Gálvez V, O'Keefe E, et al. Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *Acta Psychiatr Scand.* 2016;134(1):48–56.
20. Grange JT, Corbett SW. Violence against emergency medical services personnel. *Prehosp Emerg Care.* 2002;6(2):186–190.
21. Maguire BJ, Smith S. Injuries and fatalities among emergency medical technicians and paramedics in the United States. *Prehosp Disaster Med.* 2013;28(4):376–382.

https://doi.org/10.1017/S1049023X21000236 Published online by Cambridge University Press