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Fixed dose ketamine for prehospital management of hyperactive delirium with severe agitation

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ABSTRACT

Introduction: Patients exhibiting signs of hyperactive delirium with severe agitation (HDSA) may require sedating medications for stabilization and safe transport to the hospital. Determining the patient's weight and calculating the correct weight-based dose may be challenging in an emergency. A fixed dose ketamine protocol is an alternative to the traditional weight-based administration, which may also reduce dosing errors. The objective of this study was to evaluate the frequency and characteristics of adverse events following pre-hospital ketamine administration for HDSA.

Methods: Emergency Medical Services (EMS) records from four agencies were searched for prehospital ketamine administration. Cases were included if a 250 mg dose of ketamine was administered on standing order to an adult patient for clinical signs consistent with HDSA. Protocols allowed for a second 250 mg dose of ketamine if the first dose was not effective. Both the 250 mg initial dose and the total prehospital dose were analyzed for weight based dosing and adverse events.

Results: Review of 132 cases revealed 60 cases that met inclusion criteria. Patients' median weight was 80 kg (range: 50-176 kg). No patients were intubated by EMS, one only requiring suction, three required respiratory support via bag valve mask (BVM). Six (10%) patients were intubated in the emergency department (ED) including the three (5%) supported by EMS via BVM, three (5%) others who were sedated further in the ED prior to requiring intubation. All six patients who were intubated were discharged from the hospital with a Cerebral Performance Category (CPC) 1 score. The weight-based dosing equivalent for the 250 mg initial dose (OR: 2.62, CI: 0.67–10.22) and the total prehospital dose, inclusive of the 12 patients that were administered a second dose, (OR: 0.74, CI: 0.27, 2.03), were not associated with the need for intubation.

Conclusion: The 250 mg fixed dose of ketamine was not >5 mg/kg weight-based dose equivalent for all patients in this study. Although a second 250 mg dose of ketamine was permitted under standing orders, only 12 (20%) of the patients were administered a second dose, none experienced an adverse event. This indicates that the 250 mg initial dose was effective for 80% of the patients. Four patients with prehospital adverse events likely related to the administration of ketamine were found. One required suction, three (5%) requiring BVM respiratory support by EMS were subsequently intubated upon arrival in the ED. All 60 patients were discharged from the hospital alive. Further research is needed to determine an optimal single administration dose for ketamine in patients exhibiting signs of HDSA, if employing a standardized fixed dose medication protocol streamlines administration, and if the fixed dose medication reduces the occurrence of dosage errors.

1. Introduction

In the prehospital setting, undifferentiated patients presenting with hyperactive delirium with severe agitation (HDSA) may be acutely disoriented, restless, aggressive, hyperthermic, and a risk to themselves or others [1,2]. These patients may initially require sedating medications for stabilization and transport to the hospital [3]. Antipsychotics

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and benzodiazepines, often considered first-line medications for sedation, may not be optimal for such patients because of their time of onset and potential adverse effects, including respiratory depression and loss of airway control [1,3,4].

Ketamine has been shown to more rapidly provide sufficient sedation within three-to-five minutes when administered via intramuscular (IM) injection, when compared to midazolam and haloperidol [3,5-7]. Ketamine is a schedule III non-narcotic that can be used to provide rapid sedation with preserved respiratory function through antagonism of glutamate *N*-methyl-D-aspartate receptors in the central nervous system, inducing a dissociated state resulting in analgesia and amnesia [8,9]. Use of ketamine for patients exhibiting signs of HDSA in the prehospital environment is considered off-label, therefore no standardized FDA approved dosing scheme exists for this indication [6,10]; however, a weight-based dose of 3–5 mg/kg of ketamine is commonly cited in the literature [6,9,11,12].

The prehospital use of ketamine in patients with altered mentation or for behavioral conditions is rare; a systematic review reported ketamine use for profound agitation in 6 out of every 10,000 patients [13]. Assessing a patient's weight and calculating the correct weight-based dose may be challenging, especially during an emergency [11,14-16]. Much of the existing literature regarding weight-based dosing is based on the pediatric population [15,17-19]. The requirement for emergency medical services (EMS) personnel to ascertain adult weights and administer appropriate weight-based dosages arises less frequently but remains equally demanding [14,20].

Paramedics faced with patients displaying signs of HDSA contend with multiple stressors, which may result in task saturation. Conventional dosing protocols may exacerbate this cognitive strain by requiring weight estimation and arithmetic computations [11,15,16,20]. To reduce cognitive load, certain medication administration protocols have the potential to be refined for time-sensitive emergencies to accelerate delivery speed and alleviate the cognitive burden on EMS personnel [15,21]. Refined protocols have the potential to enhance patient safety, mitigate the risk of medication dosing errors, and streamline the administration of therapeutic medications [15,21].

The New York State Collaborative EMS Protocols call for a fixed dose of 250 mg IM on standing order for the treatment of agitated adult patients who are extremely combative and are at immediate risk of causing physical harm to themselves and/or others [22]. The primary objective of this study was to determine the safety of a 250 mg fixed dose protocol by evaluating the frequency of adverse events following pre-hospital ketamine administration for HDSA. The secondary objectives were to describe the characteristics of these ketamine-related adverse events, to assess their impact on patient outcomes, and to determine the corresponding weight-based dose in a cohort of prehospital patients with severe agitation.

2. Methods

This was a single hospital, multiagency, retrospective chart review to examine the use of fixed dose IM ketamine for the prehospital treatment of HDSA. During the period studied (January 2019 – December 2021), patients exhibiting signs of HDSA were treated based on a protocol entitled, "Excited Delirium" [23]. Prehospital and hospital medical records of patients who received fixed dose 250 mg IM ketamine in the prehospital setting for HDSA based on standing orders from the "Excited Delirium" protocol were reviewed. Dosing ratios for the 250 mg IM ketamine were calculated based on reported body weight to determine how they corresponded to the weight-based dose for each patient. Participating agencies included four Advanced Life Support (ALS) EMS agencies, each of whom fall under the oversight of the same regional emergency medical advisory committee and follow a common set of patient care protocols. The study was approved by the University at Buffalo Institutional Review Board (IRB).

EMS records were electronically screened for incidents of ketamine use from January 2019 (when ketamine first became available for prehospital use under state and regional protocols) through December 2021. The prehospital and hospital medical records for these encounters were reviewed by study team members for the full inclusion and exclusion criteria. Cases were included if the patient was 18 years of age or older and had received 250 mg IM ketamine on standing order (Fig. 1). Patients who received ketamine via direct medical oversight in consultation with a physician, were transferred between hospitals, or received ketamine for any other purpose (e.g., pain, rapid sequence induction, post-intubation sedation) were excluded from the analysis (Fig. 1).

All charts were reviewed by a dually board-certified emergency medicine (EM) and EMS physician. Information regarding the administration of additional sedating medications by EMS or in the ED, and ventilatory supporting interventions were extracted from the patient records (Fig. 1). Hospital discharge records were reviewed for patient outcomes.

The equivalent weight-based dose was calculated by dividing the prehospital ketamine dose by the patient's weight recorded in the hospital record. For patients who received multiple doses of ketamine in the field, only the first dose was included in the primary weight-based analysis. The statistical analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC). Descriptive statistics and logistic regression model were used to analyze the data. A stepwise variable selection was conducted on a list of covariates, including sex, age, toxicology, and hospital medication administered. All covariates were not significant at 0.05. The logistic regression model with two key variates: calculated weight-based initial dose (250 mg) and calculated weight-based total dose (total administered), which includes the additional 250 mg dose received by 12 patients. Normally distributed values were expressed using (mean ± SD), other continuous values were expressed using (mean, IQR). The normality was examined using Shapiro-Wilk test. Statistical significance was set at $p \leq 0.05$.

3. Results

There were 132 patient encounters identified through the query of EMS records for ketamine administration. Sixty (60) cases met the inclusion criteria and were analyzed. Forty-five (75%) patients were male. The patients' median age was 34.5 years old (range: 19–72 years), mean age 36.3 years old (IQR:14.5 years) (Fig. 2). The median weight was 80 kg (range: 50–176 kg), mean weight (86.3, IQR: 31.8). The initial 250 mg fixed dose of ketamine was equivalent to <3.0 mg/kg for 25 (42%, 1.4–2.9 mg/kg) patients and 3.0–5.0 mg/kg for 35 patients (58%, 3.1–5.0 mg/kg) patients (Fig. 3). The initial fixed dose of ketamine used was not >5 mg/kg for any patient.

Of the initial 60 patients who received a fixed dose of 250 mg ketamine in the field for severe agitation, 12 (20%) were given a second 250 mg fixed dose of ketamine by EMS personnel for a total of 500 mg (Fig. 1). Five patients that received second doses received a total ketamine dose >5 mg/kg, with the highest recorded at 7.3 mg/kg. None of those that received a second dose of ketamine from EMS had an adverse event or were intubated. Two patients received 5 mg IM midazolam, and one patient received 10 mg IM midazolam [22], prior to being administered a fixed dose of ketamine, none of whom were subsequently intubated (Fig. 1).

No patients were intubated by EMS in the prehospital setting following ketamine administration. Three patients (5%) received ventilatory support with a bag-valve mask (BVM) from EMS in the prehospital setting, including one due to laryngospasm following the administration of ketamine by the paramedic. One patient (1.7%) was orally suctioned by EMS for frothy secretions after administration of ketamine in the prehospital setting but did not require intubation or any other interventions (Table 1).

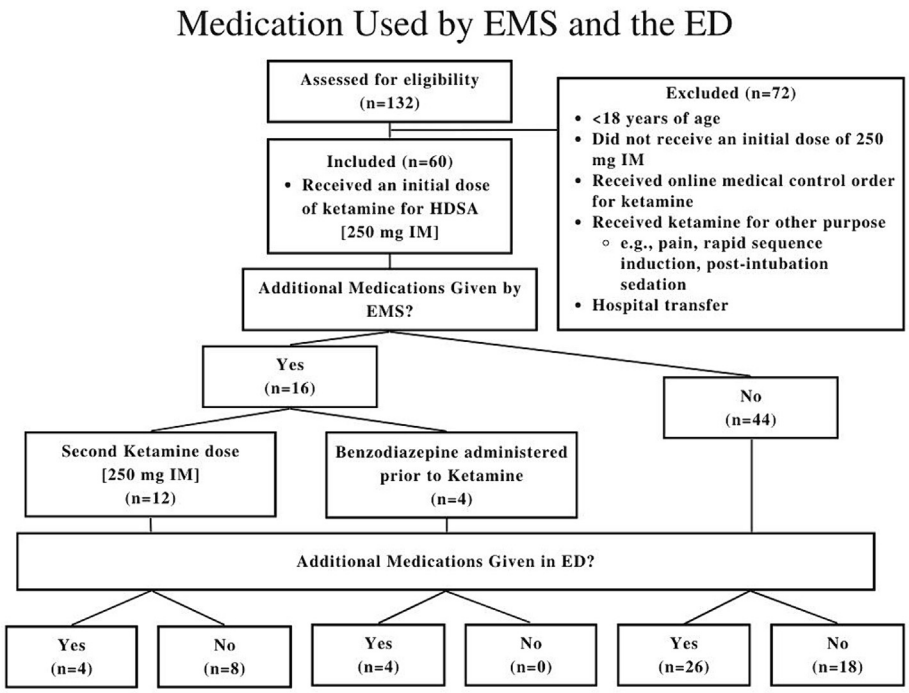

Fig. 1. Administration of additional medications in prehospital or ED settings for patients receiving at least one dose (250 mg) of ketamine by EMS personnel in the prehospital setting.

Six (10%) patients were intubated in the ED, including the three (5%) who received ventilatory support from EMS, and three (5%) others that did not received ventilatory support from EMS, but received additional parenteral sedation in the ED prior to intubation. All six of the intubated patients were initially admitted to the ICU and subsequently discharged from the hospital with a Cerebral Performance Category (CPC) 1 score. Among the patients who were intubated in the ED, the 250 mg fixed dose of ketamine equated to 2 mg/kg for 1 (17%) patient, 3 mg/kg for 2 (33%) patients, 4 mg/kg for 2 (33%) patients and 5 mg/kg for 1 (17%) patient. One of the six patients was sedated further and intubated to facilitate advanced imaging, not due to respiratory failure (Table 1).

A logistic regression model examined the effects of the calculated weight-based initial dose (250 mg) and calculated total prehospital weight-based dose on risk of intubation. The weight-based dosing equivalent was not associated with the need for intubation (OR: 2.62, CI: 0.67–10.22) (Table 2). The same logistic regression model also examined the calculated total prehospital weight-based dose, including those patients who received a second 250 mg dose ($n = 12$ patients; 500 mg total), on risk of intubation. Similarly, the confidence interval for the adjusted odds ratio of intubation associated with one-unit increase in total prehospital dose (OR: 0.74, CI: 0.27, 2.03), also suggesting there is no statistically significant association (Table 2).

4. Discussion

Current protocol permits EMS personnel to administer a single 250 mg fixed dose of ketamine. It also allows for a second 250 mg dose if the first dose is not effective. 80% of the patients in our study only required a single 250 mg dose of ketamine while 20% did receive a second 250 mg dose. No patients were intubated by EMS and no deaths occurred among the patients studied. These data suggest that a fixed dose of 250 mg IM ketamine is an effective alternative to weight-based dosing for adult patients exhibiting signs of HDSA.

Ketamine is infrequently administered in the prehospital environment, and when administered, it is often in a high stress situation, compounding the risk of a weight-based dosing error [11,20,24].

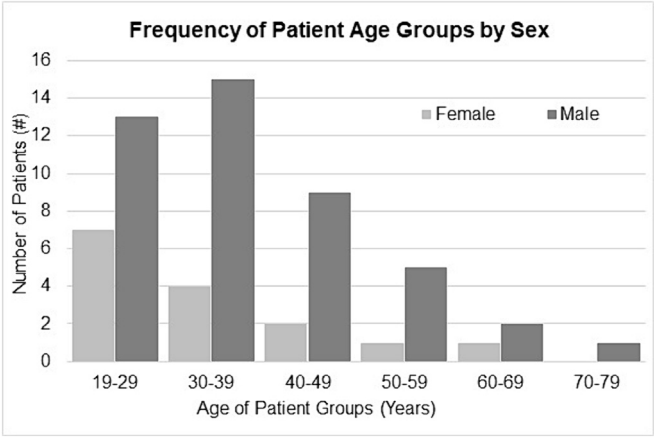

Fig. 2. Frequency of patients' ages in years by age groups and sex.

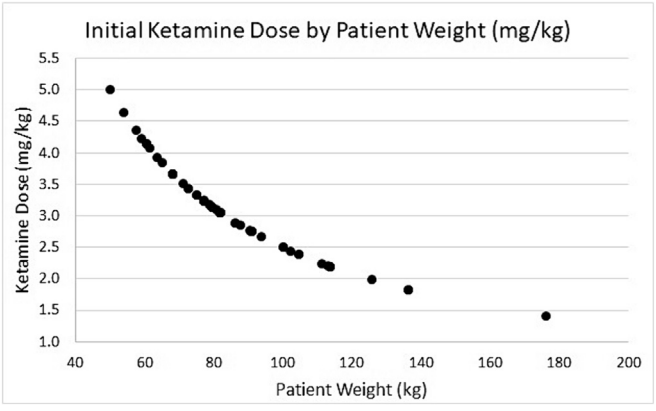

Fig. 3. Initial ketamine dose administered in the field by EMS personnel displayed as relative (mg/kg) and absolute (mg) values by patient weight (kg).

Table 1
Prehospital and hospital adverse events (AE) for patients who received 250 mg fixed dose of Ketamine from a paramedic in the prehospital setting. One patient (*) also received two doses of Midazolam 5 mg IM from a paramedic in the prehospital setting. Emergency Department (ED). Methicillin-resistant *Staphylococcus aureus* (MRSA)

	Prehospital Ketamine Dose mg (mg/kg)	Prehospital AE Intervention	Hospital AE Intervention	Urine Tox	ETOH	Comments
1	250 (3.1)*	Laryngospasm BVM	Laryngospasm Intubation upon arrival	Benzodiazepines Cannabinoids	Negative	Unremarkable hospitalization
2	250 (4.6)	Apnea BVM	Apnea Intubation upon arrival	Negative	Negative	MRSA pneumonia with parapneumonic effusion
3	250 (3.9)	Respiratory depression BVM	Respiratory failure Intubation upon arrival	Cannabinoids	Negative	Unremarkable course, extubated and signed out against medical advice
4	250 (4.2)	Frothy secretions Suction	None	Not Tested	288 mg/dL	Unremarkable ED course, discharged to emergency psychiatric program
5	250 (2.8)	None	Sedated Intubation	Benzodiazepines Cannabinoids	Negative	Increased agitation Sedated and intubated to facilitate imaging after 6-h in ED
6	250 (2.2)	None	Respiratory failure Intubation	Negative	350 mg/dL	Additional ketamine administered in ED causing respiratory failure
7	250 (4.4)	None	Seizure Intubation upon arrival	Cocaine Cannabinoids	Negative	Arrived obtunded, seizure in ED, administered Ativan and fentanyl, intubated in the ED

Because of these challenges and increased ease of administration, the use of fixed dose medications are being developed, especially in prehospital care [25-27]. The use of fixed dose ketamine in emergency settings has been studied in patients with suicidal ideation (intranasal) [25] and adolescent procedural sedation in the ED (intravenous) [27], but to our knowledge, only one other study that explored prehospital fixed dose ketamine for severe agitation [26]. Isoardi, et al. (2021) examined the use of 200 mg IM fixed dose ketamine under direct medical oversight in the prehospital setting for severe acute behavioral disturbances. Their protocol required the use of ketamine as a second line medication when droperidol was ineffective. The nature of that intervention requiring direct medical oversight also allowed for alterations to the dose and route of medication administration [26].

For some patients presenting with HDSA, rapid sedation can mitigate the risk of injury, metabolic acidosis, hyperthermia, and rhabdomyolysis, among other medical conditions [1,5,9]. The effectiveness and reliability of ketamine to achieve sedation in patients with HDSA has been reported at 90–98% [5,9,26,28]. Ketamine also has a relatively rapid onset, typically within 5 min, in comparison to other medications, which can take two to three times longer [7]. The safety profile of ketamine shows effective results with minimal risk of adverse events [7,24,29]. Although there is a risk of suppressed respirations, laryngospasm, and frothy secretions, supportive management of these adverse events can be effective [26]. Adverse prehospital events in the current study were treated by EMS personnel with either oral suctioning or ventilatory assistance with a BVM; none required prehospital intubation, which is consistent with other studies (Table 1) [30]. Overall, the post ketamine administration intubation rate in the current study of 10% was consistent with or below what has been reported in the existing literature [11,20,30-33]. While six patients were ultimately intubated in the ED, half of them received additional sedating medications in the ED prior to intubation. Additional patient and physician factors may have influenced the decision to intubate in the ED (Table 1) [11,30]. Finally, all patients who were intubated were ultimately discharged from the hospital with a CPC score of 1, indicating a return to pre-encounter function.

A 250 mg fixed dose of ketamine corresponds to 3 mg/kg in an 83 kg patient, and 5 mg/kg in a 50 kg patient. The lowest patient weight in our data set was 49.9 kg (Fig. 3). One potential result of this fixed dose protocol may have been to reduce the dose that would have otherwise been administered under a weight-based dosing scheme. Coffee et al. (2021) suggested that a lower weight-based dose could be effective while reducing adverse events [31]. Similar to prior studies, there were no associations between dose of ketamine and intubation in the current study [9,32].

During the time period studied, paramedics in the study region operated under a protocol entitled "Excited Delirium." [23] Over the past few years, this nomenclature has been phased out as part of a multifactorial; medical, psychiatric, social, and political debate [2,34-36]. Research supports the use of ketamine as safe and effective [1,6,20,24]. At the time of publication of the manuscript, paramedics in the region studied are authorized to administered ketamine 250 mg IM under a new "agitated patient" protocol "for patients who are extremely combative and are at immediate risk of causing physical harm to emergency responders, the public, and/or themselves." [22] This new protocol does not include the terminology "excited delirium" but more clearly describes the constellation of clinical signs which may necessitate this intervention.

The decision to administer ketamine is one part of what should be a multimodal response to a patient with severe agitation. The way a patient is positioned, especially during transport, is a critical factor to consider [13]. Placing patients in a prone position may expose them to a heightened risk of respiratory failure and even mortality [35,37]. The EMS protocols in the study region explicitly prohibit transport of agitated patients in a prone position [22]. The relationship between body mass and positional asphyxia has the potential to be exacerbated when an obese individual is administered larger doses of ketamine based on their weight [38]. Additionally, excessive accumulation of adipose tissue in the neck region may obstruct airflow due to body/neck positioning and/or relaxation of the musculature from sedation [6,38,39]. It is also crucial to have a proper comprehension of the role of physical restraints in ensuring patient

Table 2
Logistic regression model for the calculated weight-based dose (mg/kg) for the initial 250 mg prehospital ketamine dose and the total prehospital doses (mg/kg) inclusive of the 48 patients that only received a single 250 mg dose and the 12 patients that received an additional 250 mg dose (total: 500 mg) of ketamine

Estimates of Logistic regression model					
Effect	Estimate	Odds Ratio Estimate	95% Wald Confidence Limits		Pr > ChiSq
Calculated weight-based dose (250 mg)	0.96	2.62	0.67	10.22	0.1669
Calculated weight-based dose (Total Administered)	−0.30	0.74	0.27	2.03	0.5572

safety, but this topic falls beyond the scope of the current study [35,40].

A decline in deaths attributed to "excited delirium" in recent years may be associated with heightened education and awareness on the topic [13,41]. Ongoing efforts should focus on advancing research, refining protocols, education, and raising awareness to enhance the safety and use of prehospital ketamine for individuals presenting with HDSA.

5. Limitations

Several limitations exist in this study. No data were available regarding the specific agitation or behavioral signs and symptoms leading paramedics to select ketamine over midazolam, so no inferences could be made about ideal choice in the sedation agent. This study used the hospital weight as the gold standard for calculating the weight-based dose. Weight estimates in the ED may be prone to many of the same risks as weight estimation in the out of hospital environment.

6. Conclusion

For all patients in this study, a fixed dose of 250 mg IM ketamine was equivalent to 5 mg/kg or less of a weight-based dose. Four adverse events were reported in the field, including three requiring ventilatory support via BVM by EMS. No patients were intubated by EMS. 10% of patients were intubated in the hospital, 5% likely due to prehospital ketamine administration by EMS and 5% who received additional sedatives in the ED prior to requiring intubation. The 250 mg fixed dose appears to be effective as the paramedics had the option to administer a second dose if the first was not effective, but only 20% of the study patients required a second dose. There were no deaths and all patients were discharged from the hospital. Further research is needed to determine an optimal single administration dose for ketamine in patients exhibiting signs of HDSA, if employing a standardized fixed dose medication protocol streamlines administration, and if the fixed dose medication reduces the occurrence of dosage errors.

Prior presentations

Presented at the 2023 NAEMSP Annual Meeting in Tampa, FL.

CRediT authorship contribution statement

Michael C. O'Brien: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Kyle J. Kelleran:** Data curation, Formal analysis, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Susan J. Burnett:** Conceptualization, Writing – original draft, Writing – review & editing. **Kaylee A. Hausrath:** Data curation, Investigation, Writing – review & editing. **Mary S. Kneer:** Data curation, Investigation, Writing – review & editing. **Nan Nan:** Formal analysis, Validation, Writing – review & editing. **Chang-Xing Ma:** Formal analysis, Validation, Writing – review & editing. **Robert W. McCartin:** Methodology, Resources, Writing – review & editing. **Brian M. Clemency:** Writing – review & editing, Writing – original draft, Conceptualization, Methodology, Project administration, Supervision.

Declaration of competing interest

None.

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