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RESEARCH REPORT

PREHOSPITAL USE OF KETAMINE VERSUS MIDAZOLAM FOR SEDATION IN ACUTE SEVERE AGITATION

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ABSTRACT

Objective: Acute severe agitation often requires pharmacologic sedation. While benzodiazepines and antipsychotics are traditional first-line medications for this purpose, recent evidence has shown that prehospital intramuscular (IM) administration of ketamine results in rapid, effective sedation. However, ketamine may be associated with adverse clinical events including a higher intubation rate. The purpose of this study is to compare the efficacy and safety of IM ketamine versus IM midazolam as medications to achieve sedation in the prehospital setting.

Methods: This is a retrospective cohort study of agitated patients with an initial Richmond Agitation-Sedation Scale (RASS) score of at least 3, who were sedated and transported by ambulance to Hartford Hospital. The primary endpoint was incidence of endotracheal intubation occurring during transportation and within one hour after arrival to the emergency department (ED). Secondary endpoints included the percentage of patients who achieved an improved RASS score post drug administration, the use of additional sedating agents and the need for airway and breathing support, and differences in adverse events.

Results: 66 patients in the ketamine group and 68 patients in the midazolam group met inclusion criteria. While more patients in the midazolam group achieved target RASS score of -1, 0, or 1 post drug administration, patients in the ketamine group had a lower mean RASS score post drug administration. There was no difference in endotracheal intubation rates between the two groups (6.1% versus 2.9%, respectively; p = 0.383). However, upon arrival to the ED, more patients in the ketamine group required additional sedating agents as well as airway or respiratory support.

Conclusion: Both ketamine and midazolam are relatively safe and efficacious in the prehospital environment. IM ketamine resulted in deeper sedation without increasing intubation rate. However, ED providers receiving patients treated with IM ketamine should prepare for additional sedating agents and airway interventions.

INTRODUCTION

Acute agitation commonly occurs in the prehospital setting. In severe cases, patients may progress to developing life threatening agitation, a complex and incompletely under-

stood physiologic process of autonomic dysfunction. Acute severe agitation is life threatening and may progress to include mania, delirium, catatonia, or respiratory or cardiac arrest (Takeuchi et al., 2011). Sudden death is thought to result from profound metabolic acidosis and catecholamine surges causing cardiac dysrhythmias (Mash, 2016).

Patients with acute severe agitation can pose a significant threat to themselves and to caregivers, necessitating chemical sedation. The profile of an ideal medication would be one that is easy to administer, with a rapid onset of action, that provides adequate duration of effect, and has a wide therapeutic window (Keseg et al., 2015). Traditional first-line therapies include benzodiazepines and antipsychotics. However, there are issues with using these classes of medications for acute severe agitation: antipsychotics have a delayed onset of action, and benzodiazepines can cause over-sedation and respiratory depression at high doses (Mash, 2016). Due to these limitations, there is emerging interest in finding an alternative sedative. Recent evidence has supported the use of intramuscular (IM) ketamine (Takeuchi et al., 2011).

Ketamine is a dissociative anesthetic agent that is often utilized for procedural sedation in the hospital setting. It works by blocking N-methyl-D-aspartate receptors, inhibiting nitric oxide synthase, and interacting with opioid receptors. The onset of IM ketamine is 3-4 minutes and sedation generally lasts 5-30 minutes (Takeuchi et al., 2011 and Linder et al., 2018). Reported adverse effects of ketamine include increased heart rate and blood pressure, hypersalivation, laryngospasm, and emergence reaction (Vien and Chhabra, 2017). Connecticut Statewide Emergency Medical Services (EMS) Protocols include ketamine for chemical restraint for " extreme agitation/combativeness" at 4 mg/kg IM with a maximum initial dose of 500 mg.

Several published studies have evaluated ketamine's efficacy and safety in managing acute severe agitation in the prehospital setting. The corresponding data has shown that ketamine results in rapid effective sedation (Ho et al., 2013 and Olives et al., 2016) and is superior to haloperidol (Cole et al., 2016). However, there was a high intubation rate in patients receiving ketamine, as high as 57% (Cole et al., 2018) and 63% (Olives et al., 2016). While a recent meta-analysis revealed a pooled intubation incidence of 1% prehospitally and 19% in the ED (Lipscombe et al., 2022), additional safety and efficacy data is necessary as ketamine is increasingly used. The purpose of this study is to compare IM ketamine versus IM midazolam when used by paramedics as sedating agents for acute severe agitation in the prehospital setting.

METHODS

Study design

This was a retrospective cohort study of patients with acute severe agitation who were transported by paramedics to Hartford Hospital between February 9, 2017 and July 31, 2018. Human subjects approval was granted by the Hartford Hospital Institutional Review Board: E-HCC-2018-0190. Hartford Hospital is a tertiary care facility and Level I Trauma Center. While chart reviewers were not blinded to the study, data taken from the hospital chart was limited to objective, documented interventions or test results.

Drug administration during ambulance transport followed the Connecticut Statewide Emergency Medical Services (EMS) protocols and medication selection was made by

provider judgement. Paramedics previously completed didactic education regarding ketamine administration and were required to submit quality assurance (QA) data forms for any ketamine or midazolam administration. QA form completion was confirmed by matching controlled drug use records to data forms, and QA data forms were used to identify all eligible patients.

The Richmond Agitation-Sedation Scale (RASS) was selected to quantify medication indication and efficacy. RASS is a 10-point scale ranging from combative (4) to unarousable (-5) (Ely et al. 2003). This assessment tool is relatively novel in the prehospital field and is more pertinent to measuring the effects of sedation and analgesia than the more common Glasgow Coma Scale (GCS). Patients were enrolled if they were between 18 and 89 years old and had profound agitation with an initial RASS score of at least 3 requiring IM ketamine or IM midazolam.

RASS was assessed at patient contact and repeated at ED triage. Patients were excluded if they were transported to a hospital other than Hartford Hospital as their ED records were unobtainable. Study data was obtained from the Hartford Hospital EMS Sedation/Analgesia Quality Assurance Form and inpatient medical records. Patient demographics, ketamine and midazolam doses, use of additional sedating agents, airway and breathing supports, endotracheal intubation during transportation and within one hour after arrival at the ED, and urine toxicology screening to identify polysubstance use as a variable were collected. Patient's hospital disposition, patient's RASS before and after sedation, and reported adverse events were also obtained.

Outcomes

The primary endpoint was the incidence of endotracheal intubation occurring during transportation and within one hour after arrival to the ED. Secondary endpoints included percentage of patients who achieved an improved RASS score of -1, 0, or 1 post drug administration, the use of additional sedating agents, airway and breathing supports during transportation and within one hour after arrival at the ED, and reported adverse events.

Study analysis

Descriptive statistics were used for both study groups. Group sample sizes of 70 in the ketamine group and 70 in the midazolam group (a total sample of 140) were predicted to afford 80% power to detect a difference between the group proportions of 0.15, using a two-sided Z test with pooled variance and a significance level of 0.05. Continuous variables were reported as mean and standard deviation, or median with interquartile range, depending on distribution while categorical variables were reported as a frequency, using percentage. A Pearson chi square test was used to evaluate the primary and secondary outcomes.

RESULTS

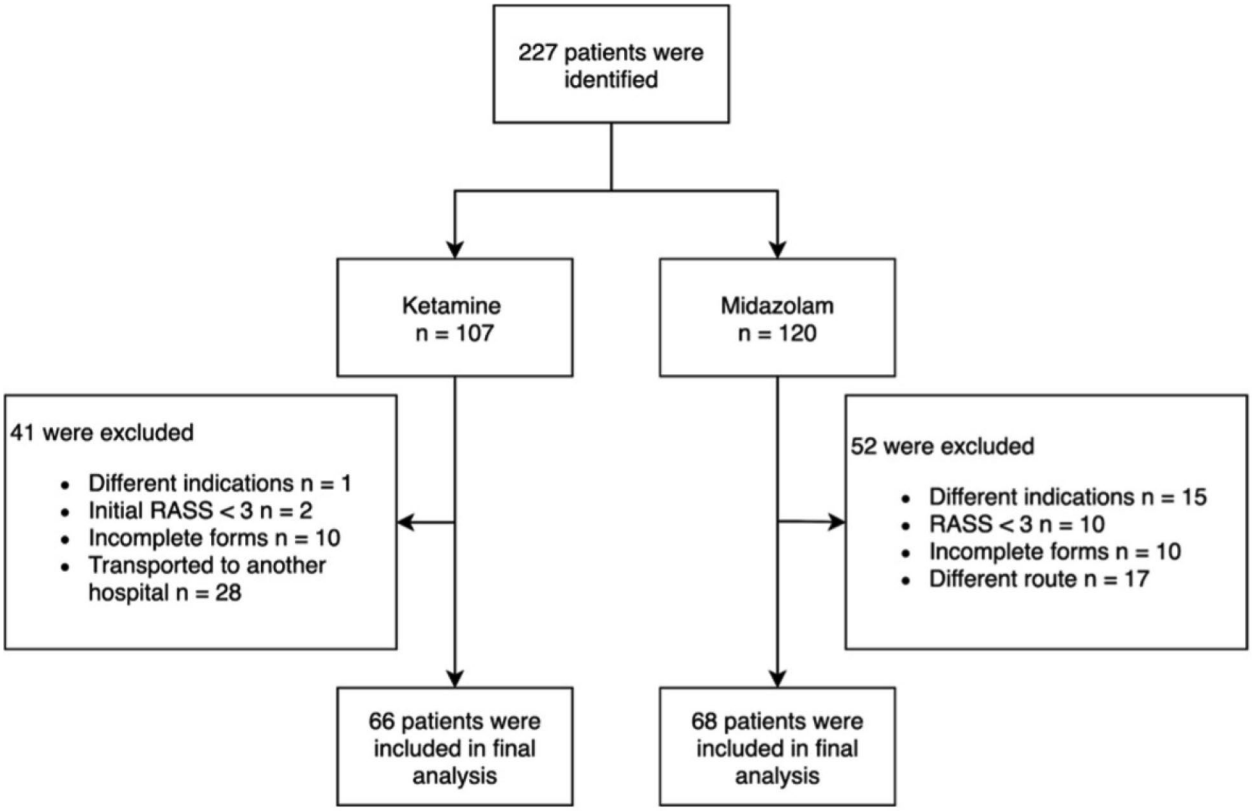

Figure 1. Results.

Patient characteristics

A total of 227 patients were identified. After applying the inclusion and exclusion criteria, 68 patients in the midazolam group and 66 patients in the ketamine group were included in the final analysis (Figure 1). The mean dose of ketamine was 288 mg (3.32 mg/kg), and the mean dose of midazolam was 5.6 mg (0.066 mg/kg). There were no statistically significant differences in baseline characteristics between two groups except for ages and RASS scores (Table 1). Patients in the ketamine group had a mean age of 35 years and patients in the midazolam group had a mean age of 44 years ($p < 0.001$). Mean initial RASS score was higher in the ketamine group (3.88 versus 3.63, $p < 0.001$).

Study outcomes

More patients in the ketamine group had an incidence of endotracheal intubation within one hour of transport to the hospital, but the result was not statistically significant (6.1% versus 2.9%, $p = 0.383$). A total of 41 patients achieved an improved RASS score of -1, 0, or 1 post drug administration. Thirteen patients (19.7%) were in the ketamine group and 28 patients (41.2%) were in the midazolam group ($p = 0.007$). Patients in the ketamine group had a deeper mean RASS score post drug administration as compared to patients in the midazolam group, overshooting target RASS of -1, 0, or 1 (-2.38 versus -0.62, $p < 0.001$). There was no statistically significant difference between the two groups concerning the use of additional sedating agents during transport. However, upon arrival to the

	Ketamine	Midazolam	p-Value
Baseline Characteristics			
Female sex - no. (%)	29 (43.9)	32 (47.1)	0.717
Age (yr)- mean ± SD	35 ± 10.4	44 ± 17.1	< 0.001
Urine toxicology collected - no. (%)	44 (66.7)	33 (48.5)	0.034
Discharged from the ED - no. (%)	42 (63.6)	49 (72.1)	0.296
Initial RASS- mean ± SD	3.88 ± 0.33	3.63 ± 0.49	< 0.001
Primary Outcome			
Endotracheal intubation- no (%)	4 (6.1)	2 (2.9)	0.383
Secondary Outcomes			
RASS of -1, 0, 1 post drug administration - no.(%)	13 (19.7)	28 (41.2)	0.007
Additional sedating agents during transport - no.(%)	19 (28.8)	19 (27.9)	0.913
Additional sedating agents within 1 hour of ED arrival - no.(%)	24 (36.4)	12 (17.6)	0.015
Additional airway supporting devices - no.(%)	30 (46.2)	10 (14.7)	< 0.001
Adverse events- no.(%)	6 (9.1)	0 (0)	0.011

Table 1. Patient Characteristics.

ED, more patients in the ketamine group required additional sedating agents and airway supporting devices as compared to patients in the midazolam group (36.4% versus 17.6%, p = 0.015 and 46.2% versus 14.7%, p < 0.001 respectively). There were also more reported adverse events in the ketamine group (9.1% versus 0%, p = 0.011), including apnea and increased oral secretions. One patient experienced a suspected emergence reaction: a complication providers should consider in the context of ketamine pharmacokinetics (Perumal et al. 2015).

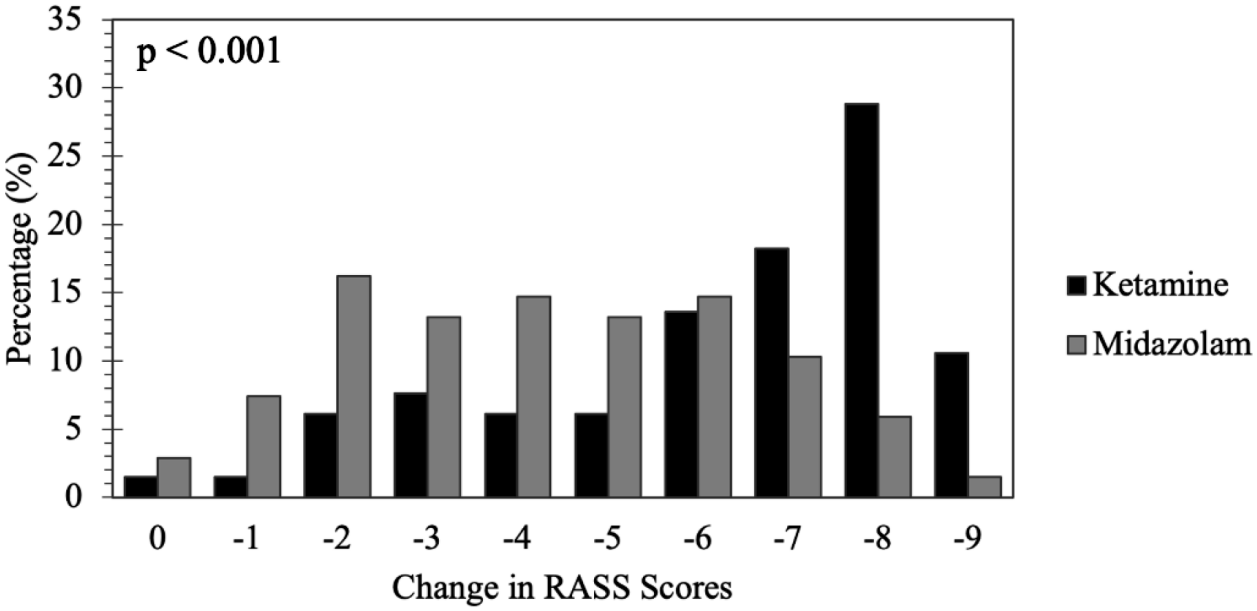

Figure 2. Change in RASS following sedative administration.

DISCUSSION

The rate of intubation was not statistically different between IM ketamine and IM midazolam, though a small absolute increase of intubation in the ketamine arm was noted (6.1% and 2.9%, respectively). This is a significantly lower intubation rate than most previous reports, which may be related to the overall lower mean dose of ketamine used in our study participants (3.3 mg/kg). Early literature on this topic correlated airway compromise with higher ketamine dose (Burnett et al. 2015). Guidance provided to paramedics was to err on the lower side of the dosing range given the inherent difficulty in prehospital weight estimation (Wells et al. 2023) and the dangers of excessive ketamine dosing. This practice may have been the key to a lower intubation rate than previous studies and may represent an effective dose for single administration sedation while avoiding negative effects.

Four different providers were involved in the four cases of intubation associated with ketamine, suggesting a low likelihood of variation in individual practice. Due to the nature of retrospective chart review, specific details on indications of intubations and the use of additional airway support were not available. Further review into the intubated patients showed that one patient was in respiratory distress prior to ketamine administration, two patients experienced hypoxemia and poor airway protection following ketamine administration, and one patient was intubated to facilitate computed tomography (motion control) after significant trauma.

In terms of efficacy, more patients in the midazolam group achieved a goal RASS of -1, 0, or 1 compared to patients in the ketamine group. When the changes in RASS scores were analyzed individually, the data showed that ketamine resulted in deeper sedation (Figure 2). Upon arriving to the ED, patients in the ketamine group were more likely to receive additional sedating agents. This may be due to ketamine having a shorter duration of action than midazolam, or it could be due to patients in the ketamine group experiencing emergence reactions that required additional sedation. Furthermore, while urine toxicology screen was performed on a subset of patients to determine confounding effects of polypharmacy, it was not performed with enough regularity to gain insight as to the effects of polypharmacy/intoxicants.

Acknowledging that an age difference was identified between groups, there may be confounding biases or variables in clinical presentation that may warrant future study. No explicit instructions were given to paramedics regarding medication selection, except to "consider dose reduction in the frail or debilitated patient." In contrast to prior literature (Holland et al. 2020), a difference in medication selection by gender was not identified.

LIMITATIONS

This was a single site retrospective chart analysis that reviewed the use of ketamine and midazolam for prehospital treatment of acute severe agitation, performed as a surveillance measure after the addition of ketamine to the regional protocols. Thus, both groups are considered standard of care and group selection was made by provider preference without randomization or resource limitation. This project is limited in capturing the total usage of ketamine or midazolam in the region, as there are several receiving facilities within close proximity. More patients in the ketamine group were transported to a different tertiary care facility, which was geographically closer for one of the enrolled

services. While our study was just shy of meeting the enrollment goal, a post-hoc sample size calculation with our data predicts n=658 patients per group would be required to meet statistical significance for intubation incidence with α=0.05, β=0.20, and 80% power.

CONCLUSION

In this study of 134 patients with acute severe agitation, the rate of endotracheal intubation between prehospital use of IM ketamine and IM midazolam was not statistically significant. Ketamine resulted in deeper sedation compared to midazolam, and more patients in the ketamine group required additional sedating agents and airway support in the ED. While these data suggest ketamine may be safer than previously reported, there are lingering challenges with dose and duration of action that infrequently require airway management. Furthermore, additional investigation is warranted to compare a larger population of patients in a prospective fashion.

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