IS KETAMINE AN EFFECTIVE SEDATIVE IN THE ACUTELY AGITATED PATIENT IN THE PREHOSPITAL SETTING?

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Abstract

Background and Significance: Cases of Excited Delirium Syndrome have been increasing in association with the use of stimulants, and is a likely cause of sudden cardiac death in patients under simultaneous physical restraint Our aim was to assess the effectiveness of ketamine compared to midazolam as a sedative through a pre-administration and post-administration data collection tool, using a modified Ramsay sedation scale, and secondarily identify factors associated with the need for airway support.

Research Question: Is IV/IM ketamine administration to patients with an acute agitated delirium more effective at sedation than Midazolam alone for prehospital transport to an acute care facility?

Methods: We conducted a prospective observational study of patients, 18 years or older, who received emergency medical assistance from paramedics over a 4-month period and received ketamine for sedation in the setting of an acute agitated delirium. In order to establish a mode of comparison, we created an additional pre-survey to identify a subgroup of paramedics who had also previously administered midazolam for the purpose of sedation in an acutely agitated patient and asked them which medication they prefer. Sedation was defined as a decrease in patient arousal that permits a safe transport and any necessary medical intervention.

Results: N=55, median dose 400mg, effective sedation was achieved in 92.73% of patients. Airway compromise was noted in 8/55 patients (14.55%), and 3 required endotracheal intubation. A potentially predictive factor associated with intubation was onset of action less than 2 minutes (p value = 0.065, trending toward significance). On-scene evidence suggestive of concurrent use of CNS depressants as reported by paramedics was present in 49.09% of patients but was not predictive for time of sedation onset or airway compromise. The level of agitation did not correlate with level of sedation after receiving ketamine or the need for airway support. Eighty-two paramedics had previously given midazolam for sedation of an agitated patient and 53 (64.6%) felt that it was effective. Sixty-two (89.86%) prefer to use ketamine over midazolam for sedation of the agitated patient.

Conclusion: Ketamine is an effective sedative in 92.73% of adult patients presenting with agitated delirium; however, a rapid onset of sedation should make the provider suspicious for impending respiratory failure particularly if they required an additional dose. Additionally, prehospital providers found ketamine to be more effective at sedation and prefer it's use over midazolam.

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Introduction/Significance

Excited Delirium Syndrome (ExDS) is described as a disorder characterized by hallucinations, aggressive and peculiar behaviors, a catecholaminergic surge and secondary risk for sudden cardiac death (Gerold, 2015). A chronic disorder, Bell's Mania, similar to ExDS in symptomatology was described by Luther Bell in 1849; other identifiers such as manic delirium, fulminating psychosis or exhaustive syndrome referred to this condition as well. With the development of sedatives and antipsychotics the incidence declined greatly until 1980s. During the 1980s to 2005, the use of stimulants such as cocaine and methamphetamines increased, as did the rates of "undetermined cause of death" in patients who were in custody and exhibited signs and symptoms of an acute agitated delirium. It was concluded that patients in this state may be in danger of avoidable death. Emergent medical treatment is required to prevent death, particularly in the setting of any kind of physical restraint. The use of restraints was found in more than half of the patients who died during retrospective review of patients with "undetermined cause of death," indicating a need for sedation that minimizes the use of physical restraint and sedates the patient chemically. Sedation decreases the chances of the toxic catecholaminergic outpouring during altercations, usually with EMS providers or police who are trying to provide medical management, that is implicated as the cause of sudden cardiac death. This disorder is recognized by The American College of Emergency Physicians (ACEP) and National Association of Medical Examiners (NAME), but has not yet been recognized by the American Medical Association (AMA) or American Psychiatric Association (APA), nor does it have its own code in the most recent ICD-10 or DSM V.

Ketamine is an excellent choice for sedation and management of this patient population, especially in the field, from an armamentarium of pharmacologic agents (Peltoniemi et al., 2016). The mechanism of action of ketamine is noncompetitive antagonism specific to NMDA receptors preventing Ca^{2+} ion influx and activation of secondary messengers and release of glutamate as well as alternate activation by glycine and glutamate, an excitatory neurotransmitter. Additionally, it is not active on opioid or GABA receptors making naloxone and flumazenil ineffective antidotes and respiratory depression unlikely. The dosing protocol

supported by the Phoenix Fire Department (1-2 mg/kg slow IV push over 1 minute or 4mg/kg IM) very closely resembles the recommended dosing by Peltoniemi et al. (2016) of 0.5-1.0 mg/kg IV bolus followed by maintenance infusion or repeated blousing or 2-4 mg/kg IM. However, the differences in the setting of administration can account for the minor differences of dosing particularly with ketamine's large therapeutic index. Although a majority of the patients in this study will not be truly suffering from ExDS, ketamine sedation and rapid management of the acutely agitated and violent patient will facilitate assessment and intervention for those who may be suffering from other emergencies including but not limited to hypoglycemia, hypoxia, overdoses of other drugs or poisons, infection or intracranial lesions or need safe transport to prevent undue harm to themselves or others. It is our goal to assess the complications associated with its use in the prehospital setting as well as to predict the likelihood and associated risk factors for respiratory failure to assist providers in their management in the future.

Materials and Methods

In this study, we evaluated whether or not Phoenix Fire Department paramedics assessments indicate that IV/IM ketamine administration to patients with Excited Delirium Syndrome is more effective at sedation than Midazolam alone for prehospital transport to an acute care facility. Additionally, we wanted to attempt to predict intubation and potentially identify risk factors that could be recognized early on to clue the paramedic into potential respiratory failure. A validated data collection tool (Figure 1) was used to assess the sedative effect of each independent ketamine administration and a comparison to midazolam (Figure 2) was established by a pre-survey which was filled out one time by each paramedic.

A data collection tool was asked to be filled out after every patient encounter by each paramedic to represent that single patients' and paramedics' ketamine experience. Seventy-five data collection tools were turned in, but 20 of them were incomplete or filled out incorrectly. Therefore, we were able to complete the data interpretation on a sample size of n=55 patients. This was considered adequate after a power analysis was completed demonstrating a need for a minimum sample size of 12.

Figure 1: Validated Ketamine Data Collection Tool

Date:		
Before Ketamine Administration		
How would you rate their level of agitation on a scale of 1-6? (circle one) • 1 – minimal (verbal de-escalation effective) • 2 - mild (oriented, uncooperative with exam) • 3 – confused (unable to follow commands) • 4 - moderate (combative) • 5 - severe (danger to self or others) • 6 - extreme (PD escort)		
Were you able to obtain vital signs?	Yes	No
Did this patient require physical restraint?	Yes	No
What **dose** and what **route** did you administer the ketamine? (circle one)	IV / IM	_____mg
Where was the IM injection site? (circle one)	Deltoid	Gluteus/ Thigh
After Ketamine Administration		
Did the vital signs (re)assessments trend toward improvement? (based on vital signs that would be classified as "normal")	Yes	No
How long until you were able to initiate the next steps in management of the patient after ketamine administration? (circle one)	**2 4 6 8 10** minutes	
How would you rate their level of sedation on a scale of 1-6 **after administering ketamine?** • 1 – asleep: **No response** • 2 – asleep: **Sluggish response** • 3 – asleep: **Brisk response** • 4 – awake: **Responds to commands** • 5 – awake: **Cooperative and oriented** • 6 – awake: **Anxious/agitated**		
Did the patient require secondary intervention related to complications of their state of agitated delirium? (ACLS, injury to self)	Yes	No
Did you give additional ketamine? (Report route and dose)	Yes	No

Did the patient require airway or ventilatory support at any time after ketamine administration or before you left the receiving facility? If **yes, circle** interventions used. ○ **BVM** ○ **LMA** ○ **OPA** ○ **ETT**	Yes	No
Did the patient require fluid resuscitation?	Yes	No
Were there any indications that the patient may have been under the influence of other CNS depressants (alcohol, opioids, benzodiazepines, barbiturates, etc.)	Yes	No
Did the patient have any of the listed adverse reactions of ketamine? If **yes, circle** all that apply. ○ **Laryngospasm** ○ **Hypersalivation** ○ **Emergence reactions (vivid dreams, hallucinations, or delirium)** ○ **Respiratory depression?**	Yes	No
In the past, have you ever administered Midazolam for the purpose of sedating a patient who was showing signs or symptoms of an acute or agitated delirium? (If yes, proceed to next question)	Yes	No
If yes, which medication do you think was more effective at sedation to allow safe intervention and transport: Midazolam or Ketamine?	Midazolam	Ketamine
Which would you prefer to give if you had the option of both?	Midazolam	Ketamine

Figure 2: Midazolam Comparison Pre-survey

Pre-survey Questions	**Yes**	**No**
1. Have you ever administered **Midazolam** to a patient with acute agitated delirium?		
2. Did you feel it was **effective at sedating** your patient to allow medical intervention?		
3. Have you ever administered **Ketamine** for acute agitated delirium?		
4. Did you feel it was **effective at sedating** your patient to allow medical intervention?		
5. Which medication did you think **was most effective** at sedation?	**Ketamine**	**Midazolam**
6. Which medication **do you prefer** to use?	**Ketamine**	**Midazolam**
7. Do you feel confident in your skills/knowledge **when using ketamine** as a sedative?		

A prospective analysis was utilized to assess EMS providers' experiences with Ketamine as the primary agent utilized in managing violent agitated and combative patients, who may also display specific signs and symptoms of ExDS. **Sedation** was defined as a decrease in patient arousal that permitted a safe environment and allowed the paramedic to assess the medical status of the patient such that at least vital signs and ECG tracing could be obtained during transport to an acute care facility.

The patients in the study received IV/IM ketamine administered by a paramedic, as indicated by the protocol written by the Medical Director with the Phoenix Fire Department. The paramedics, during every ketamine administration, were expected to follow proper documentation protocol with a minimum of, but not limited to:

- Scene assessment upon arrival and chief complaint
- Vital signs (2 sets)
    - heart rate, respiratory rate, blood pressure, temperature, pulse oximetry
- Finger stick blood glucose level
- Interventions pertaining to airway, breathing and circulation
    - Medications
        - Intravenous fluids, sedative medications, supplemental oxygen, etc.
    - Procedures
        - Positive pressure ventilation, intravenous access, cooling, etc.
- If restraints were used:
    - Reason
    - Position
    - Status of circulation distal to restraints, assessed every 10 minutes
    - Patient status at time of transfer of care
    - Total time patient was restrained
- Any obtainable past medical history, social history, allergies, medications, alcohol/tobacco/illicit drug use

After leaving the facility, the paramedic was able to participate in the data collection by filling out the survey at this time. This questionnaire was available to the administering paramedic at the fire station, in the fire engine and in the ambulance as well as at any continuing education classes for timely and convenient completion. Collection was mediated through interoffice mail and collected monthly as well as turned in after any continuing education classes.

The standardized data collection questionnaire assessed their individual experience with the use of ketamine as an effective agent to safely manage the violent, agitated or combative patient during assessment and transport. The data collection tool was validated prior to institution by giving it to the paramedics during continuing education classes taught by the Medical Director. This ensured it was interpreted uniformly and consistently across various paramedics with varying previous experiences prior to implementation in the study. The tool was adjusted until this focus was obtained through changes in the length, verbiage or flow of the questionnaire.

Statistical Analysis

The primary outcome for this analysis is whether the patients were responsive to stimuli versus those who were not after ketamine administration. Survey characteristics were assessed using means, standard deviations for continuous variables and frequencies, proportions for categorical variables. Univariate logistic regression was used to assess whether the survey characteristics were independently associated with being unresponsive post ketamine administration. All covariates with $p<0.20$ were entered into a second multivariate model to assess whether the selected covariates best predictive of post-ketamine unresponsiveness. The same procedure of univariate and multivariate logistic regression was used for the secondary outcomes of pre-ketamine agitation, and onset of Medication. All p-values were two-sided and $p<0.05$ was considered statistically significant. All data analysis were conducted using STATA version 14 (College Station, TX).

Results

A total of 152 presurveys were collected, in which 51 (33.55%) were incomplete or filled out incorrectly. Of note, within these surveys, only 87/101 (86.14%) paramedics had administered both ketamine and midazolam during their career, allowing their response to be utilized as a subject within the comparison population. Paramedics were asked to only fill out this survey once.

Data was collected from November 2016 to March 2017 and a total of 55 patients were enrolled in the study via survey completion by the paramedic who administered the ketamine. It is unknown how many patients actually received ketamine during this time frame because participation in the study was optional for the paramedic. Agitation was graded on a Likert scale from 1-6; 25/55 (45.45%) patients were deemed to have severe agitation requiring a police escort to facilitate care and transport of the patient to the hospital. Twenty-one (38.18%) were described as a danger to themselves or others, 8 (14.55%) were described as combative and 1 (1.82%) was described as being unable to follow commands. The paramedics were able to obtain vitals on 39/55 (70.91%) of the patients and the ketamine was administered intramuscularly 94.55% (52/55) of the time. Fifty patients received the intramuscular injection in the deltoid, and five patients received the dose in the vastus lateralis. Dosing was repeated in 8/55 (14.55%) patients, however the repeat dose and route was not collected.

Most administrations resulted in an onset of sedation within two minutes (26/55; 47.27%), but 34.55% (19/55) had onset within four minutes, 16.36% (9/55) had onset within six minutes, 0 reports of eight minutes and 1.82% (1/55) reported 10 minutes. Upon reassessment of the patients, 84.55% of patients demonstrated an improvement in their vital signs after sedation and on a second Likert scale, which was a modified take on the Richmond Agitation-Sedation. When classified as being asleep or awake, 85.45% were described as “asleep” and further categorized according to their response to stimulation: None (21/55, 38.18%), sluggish (21/55, 38.18%), brisk (5/55, 9.09%). Eight patients were classified as awake, and further described as

responding to commands (3/55, 5.45%, cooperative and oriented (1/55, 1.82%) or still anxious/agitated (4/55, 7.27%).

Spearman's rho (-0.0035) was performed to determine if there was a relationship between the level of agitation and the need for additional ketamine and found that they were not associated with one another. Additionally, the agitation scale in the data collection tool was not predictive of needing additional ketamine in a two-sample Wilcox rank-sum test (z = 0.9793), though repeat dosing did increase the likelihood for effect on the need for ventilatory support (Fisher's exact = 0.587). One thing to note however, is that the patient was 3.6 more likely to be unresponsive after additional dosing, and this was associated with two-fold increase in the need for ventilatory support. Lastly, their level of agitation was not associated with the patient needing secondary intervention after sedation was achieved (Spearman's rho = -0.1084, t=0.4307). This was also repeated with a two-sample Wilcoxon rank sum test without identified relationship (z = 0.4255).

The onset of sedation after ketamine administration was not associated with the patient's pre- or post-sedation scales. It was ultimately effective in 92.73% of patients despite taking up to 10 minutes to be able to provide the next steps in care. The odds ratio for pre-ketamine administration and association with onset of action was 0.38 (0.12, 1.1 with a 95%CI, p=0.08), and the post-sedation odds ratio was even more valuable with a statistically significant result of 0.27 (0.08, 0.85) with a 95% CI, p=0.02. Administration of additional ketamine did not effect the onset of action (OR 0.31, p=0.18). When using Spearman's rho (0.2503) to assess the relationship between the onset of action of ketamine and the need for airway support, the correlation was trending toward significance with a p-value of 0.0653; however, this was not supported by the odd's ratio of 0.24 (0.05, 1.4; 95% CI, p=0.10).

When airway ventilation was compared against various exposures (table 3), secondary intervention occurred in all of these patients with an OR 20.5 (3.3, 125.9, 95% CI, p=0.001). However, it is unknown if the secondary intervention was limited to just the airway support (i.e. OPA, LMA or ETT) or if there were other interventions that the data collection tool was not able to capture.

In the multivariate analysis (Table 4), most of the statistically significant data did not persist after the adjusted odds ratio. Specifically, whether or not onset of sedation after ketamine administration was correlated with the need for advanced airway support AOR 0.34(0.04, 2.9; p=0.32 and area under the curve 0.80). The pre-sedation agitation scale continued to have no relationship with the onset of sedation or final post-sedation scale with the follow AOR, respectively, AOR 0.31 (0.09, 1.04, p=0.05) and AOR 0.28 (0.08, 1.01, p=0.05) and area under the curve equal to 0.76).

When examining the data qualitatively as two independent variables, ketamine was effective at sedation and positively influenced patient care based on the data collection questionnaire results (Table 1). Ketamine expedited the time frame for intervention in 81.82% (OR 3.7; 95% CI, p=0.02) of patients by allowing initiation of care within four minutes. Additionally, ketamine was unlikely to be associated with need for ventilatory support or repeat dosing, and respectively, had an odds ratio of 0.30 (0.06, 1.4 with a 95% CI, p=0.13) and 0.19 (0.02, 1.6, with a 95% CI, p=0.13); though these results were not statistically significant.

Secondary interventions related to complications of their agitation were reported in 8/55 (14.55%) of patients but were not defined by the data collection tool. Additionally, in order to protect private health information, there was no way to follow-up on any of the individual patients or said complications. We did specifically inquire about the need for needed airway support in order to try to predict the likelihood for intubation with ketamine. Eight of the 55 patients (14.55%) were reported to need airway support, 3/8 (37.5%) of which required endotracheal intubation, 4/8 (50%) had a laryngeal mask airway placed and 1/8 (12.5%) was supported with an oral pharyngeal airway. Additionally, one person had hypotension requiring fluid resuscitation.

The paramedics were also asked if there was any indication that they patient make have been under the influence of any central nervous system depressants, such as alcohol, opioids, benzodiazepines or barbiturates. Twenty-seven of the 55 (49.09%) patients were reported as yes, and 28/55 (51.9%) did not have any indication of other potentially depressant intoxicants. A report was adverse reactions was recorded as a binary yes (5/55, 9.09%) or no (50/55,

90.91%), with the option to describe the reaction or select one of the common adverse reactions known to ketamine. Zero reports of laryngospasm occurred, 1/5 (16.67%) had hypersalivation, 1/5 (16.67%) had an emergence reaction, and 3/5 had respiratory depression (60%). One patient was described as having one of the above-mentioned adverse effects under the description "other" after the paramedic received hospital follow-up, but it is unknown which adverse reaction occurred.

At the end of the survey, the paramedics were asked to report whether or not they had given midazolam for the same purpose; 39/55 (70.91%) had reported yes, and 16/55 (29.09%) reported no. Based on those who answered yes, 37/39 (94.87%) reported that ketamine was more effective at sedation to allow safe medical intervention and transport and would also prefer to use ketamine over midazolam in this patient population.

Table 1: Sedation post ketamine administration

Survey Characteristics	Response to Stimuli N=34	Unresponsive N=21	OR (95% CI)	P-value
Pre-Ketamine Agitation (yes, %)	16 (47.1)	9 (42.8)	1.18 (0.39, 3.5)	0.76
Were you able to obtain vital signs? (yes, %)	11 (32.4)	5 (23.8)	1.53 (0.44, 5.2)	0.49
Did this patient require physical restraint? (yes, %)	32 (94.1)	21 (100.0)	N/A	
Route Administration (IM, %)	31 (31.2)	21 (100.0)	N/A	
After you administered ketamine, approximately how long until you were able to initiate the next steps in management of the patient? (≥4 min, %)	22 (64.7)	7 (33.3)	3.7 (1.2, 11.6)	0.02
Did the patient require secondary intervention related to complications of their state of agitated delirium? (yes, %)	8 (23.5)	4 (19.1)	1.31 (0.34, 5.0)	0.69
Did you give additional ketamine? (yes, %)	27 (79.4)	20 (95.2)	0.19 (0.02, 1.6)	0.13
Did the patient require airway or ventilatory support at any time after ketamine administration or before you left the receiving facility? (yes, %)	3 (8.8)	5 (23.8)	0.30 (0.06, 1.4)	0.13
Did the patient require fluid resuscitation? (yes, %)	0 (0.0)	1 (4.7)	N/A	
Were there any indications that the patient may have been under the influence of other CNS depressants? (yes, %)	16 (47.1)	11 (52.4)	0.80 (0.27, 2.4)	0.70
Did the patient have an adverse reaction to ketamine? (yes, %)	5 (14.7)	5 (23.8)	0.55 (0.13, 2.2)	0.39
In the past, have you ever administered ***Midazolam*** for the purpose of sedating a patient who was showing signs or symptoms of an acute or agitated delirium? (yes, %)	10 (29.4)	6 (28.5)	1.04 (0.31, 3.5)	0.94

Table 2: Onset of action

Survey Characteristics	< 4min Onset N=26	≥4 min Onset N=29	OR (95% CI)	P-value
Pre-Ketamine Agitation (yes, %)	15 (57.7)	10 (34.5)	0.38 (0.12, 1.1)	0.08
Were you able to obtain vital signs? (yes, %)	9 (34.6)	7 (24.1)	0.60 (0.18, 1.9)	0.39
Did this patient require physical restraint? (yes, %)	24 (92.3)	29 (100.0)	N/A	
What **route** did you administer the ketamine? (IM, %)	25 (96.2)	27 (93.1)	0.54 (0.05, 6.3)	0.62
How would you rate their level of sedation? (No Response, %)	14 (53.8)	7 (24.1)	0.27 (0.08, 0.85)	0.02
Did the patient require secondary intervention related to complications of their state of agitated delirium? (yes, %)	7 (26.9)	5 (17.2)	0.56 (0.15, 2.1)	0.38
Did you give additional ketamine? (yes, %)	24 (92.3)	23 (79.3)	0.31 (0.06, 1.7)	0.18
Did the patient require airway or ventilatory support at any time after ketamine administration or before you left the receiving facility? (yes, %)	6 (23.1)	2 (6.9)	0.24 (0.05, 1.4)	0.10
Did the patient require fluid resuscitation? (yes, %)	1 (3.9)	0 (0.0)	N/A	
Were there any indications that the patient may have been under the influence of other CNS depressants? (yes, %)	11 (42.3)	16 (55.2)	1.67 (0.57, 4.9)	0.34
Did the patient have an adverse reaction to ketamine? (yes, %)	6 (23.1)	4 (13.8)	0.53 (0.13, 2.2)	0.37
In the past, have you ever administered ***Midazolam*** for the purpose of sedating a patient who was showing signs or symptoms of an acute or agitated delirium? (yes, %)	9 (34.6)	7 (24.1)	0.60 (0.18, 1.9)	0.39

Table 3: Airway Ventilation

Survey Characteristics	No N=47	Yes N=8	OR (95% CI)	P-value
Pre-Ketamine Agitation (yes, %)	21 (44.7)	4 (50.0)	1.23 (0.27, 5.6)	0.78
Were you able to obtain vital signs? (yes, %)	13 (27.7)	3 (37.5)	1.56 (0.32, 7.5)	0.53
Did this patient require physical restraint? (yes, %)	45 (95.7)	8 (100.0)	N/A	
What **route** did you administer the ketamine? (IM, %)	44 (93.6)	8 (100.0)	N/A	
How would you rate their level of sedation? (No Response, %)	16 (34.0)	5 (62.5)	3.2 (0.68, 15.3)	0.13
Did the patient require secondary intervention related to complications of their state of agitated delirium? (yes, %)	6 (12.8)	6 (75.0)	20.5 (3.3, 125.9)	0.001
Did you give additional ketamine? (yes, %)	39 (82.9)	8 (100.0)	N/A	
After you administered ketamine, approximately how long until you were able to initiate the next steps in management of the patient? (≥4 min, %)	27 (57.5)	2 (25.0)	0.24 (0.04, 1.4)	0.10
Did the patient require fluid resuscitation? (yes, %)	0 (0.0)	1 (12.5)	N/A	
Were there any indications that the patient may have been under the influence of other CNS depressants? (yes, %)	24 (51.1)	3 (37.5)	0.57 (0.12, 2.3)	0.48
Did the patient have an adverse reaction to ketamine? (yes, %)	2 (4.3)	8 (100.0)	N/A	
In the past, have you ever administered ***Midazolam*** for the purpose of sedating a patient who was showing signs or symptoms of an acute or agitated delirium? (yes, %)	13 (27.7)	3 (37.5)	1.56 (0.32, 7.5)	0.57

Table 4: Multivariate analysis with Adjusted Odds Ratio

Predictors	AOR (95% CI)	P-value	Area Under the Curve
Sedation Rate			0.72
After you administered ketamine, approximately how long until you were able to initiate the next steps in management of the patient?	0.33 (0.10, 1.1)	0.07	
Did you give additional ketamine?	3.67 (0.39, 34.4)	0.25	
Did the patient require airway or ventilatory support at any time after ketamine administration or before you left the receiving facility?	2.04 (0.39, 10.5)	0.39	
Onset of Medication			0.76
Pre-Ketamine Agitation	0.31 (0.09, 1.04)	0.05	
How would you rate their level of sedation?	0.28 (0.08, 1.01)	0.05	
Did you give additional ketamine?	0.46 (0.07, 2.8)	0.40	
Did the patient require airway or ventilatory support at any time after ketamine administration or before you left the receiving facility?	0.33 (0.05, 2.1)	0.24	
Airway Ventilation			0.80
How would you rate their level of sedation?	7.55 (0.66, 85.7)	0.10	
Did the patient require secondary intervention related to complications of their state of agitated delirium?	42.4 (3.6, 488.9)	0.003	
After you administered ketamine, approximately how long until you were able to initiate the next steps in management of the patient?	0.34 (0.04, 2.9)	0.32	

Discussion

As expected, ketamine was well received by the paramedic population and preferred over midazolam in 89.86% of paramedics as an agent that was effective at sedation for transport of patients with concern for excited delirium syndrome. The questions in the data collection tool were analyzed independently of each other for any relationships that existed the individual questions. Only one positive association was found and is also trending toward significance; when the onset of sedation was examined in the context of the patients who required ventilatory support, it was found that an onset of less than 2 minutes may predict risk for respiratory failure (p=0.653). However, and unexpectedly, the onset of action did not demonstrate a relationship with paramedic scene assessment and clinical gestalt on whether or not the patient was under the influence of other central nervous system depressants. There was also no connection between patients in whom the paramedic suspected or saw physical evidence of other depressant medications and the risk for needing ventilatory support (Fisher's exact 0.705) or if there was a reported adverse reaction (Fisher's exact = 0.729) in the agitated patient who received ketamine. In the multivariate analysis, patient who received an additional dose of ketamine were 3.6x more likely to be unresponsive, of which these patients had a 2-fold increased risk for respiratory failure. Repeat dosing was not directly related to need to for ventilatory though, however. These important negative findings are in line with our original hypothesis and support the use of ketamine as a prehospital medication for agitated delirium, but with continued caution and need for more education by the provider.

Our study and data are similar in comparison to what already exists on prehospital ketamine in the literature. For example, in the article, "Prehospital Use of IM Ketamine for Sedation of Violent and Agitated Patients," (Scheppke et al., 2014) they had a similar sample size, n=52; however, half of the patients received midazolam IV to "prevent" emergence reactions associated with ketamine, such as hallucinations. Additionally, the study demonstrated that respiratory depression was an untoward outcome in 6% of the patients, all of which involved subsequent midazolam administration. In our study, only one patient was noted to have an emergence reaction out of 55 subjects, making it unlikely that the number needed to treat is

greater than the number needed to harm by prophylactic midazolam. Their study was also an entirely retrospective chart review without consideration of input from the paramedics who administered the medications or their assessment of the patient after the initial dose of ketamine. It is questionable whether the patients truly needed additional sedation by midazolam or if ketamine by itself was sufficient for transport and initiation of emergency medical management. The study did not discuss any untoward outcomes related to ketamine administration independent of midazolam, but this sample size is even smaller, n=26. Out larger sample size did catch an increased incidence of airway compromise (8/55 patients), potentially because of the increased number of subjects in our study.

Their limitations were similar to the limitation in our study, such as the sample size, and follow-up of outcomes upon arrival to the emergency department with or without untoward effects from the medications administered. Additionally, no statistical power methods were applied to their data sets to provide confidence intervals for their analysis. In the article, *Ketamine for pre-hospital control of agitated delirious patients: Promising but not yet ready for prime time* by Schultz (2014), a critical examination was performed of the study by Scheppke et al. (2014) and listed similar reservations related to the methods used and an increased need for more research to establish if ketamine is truly a safe and effective treatment for this vulnerable patient population.

Another study, "The Use of Prehospital Ketamine for Control of Agitation in a Metropolitan Firefighter-based EMS System," by Keseg et al. (2015) evaluated the use of ketamine as a sedative for combative patients administered by paramedics. The efficacy and safety of the drug in this setting was evaluated with retrospective chart review as well on an even smaller sample size, n=35, that had more specific parameters than the study by Scheppke (2014), but was of little contribution due to the binary questionnaire utilized to evaluate "improve[ment]." Additionally, an EMS liaison between the hospitals who received these patients and the EMS system were able to contribute more data to further investigate patient outcomes upon arrival to the emergency department. The limitation of this study includes the lack of identification of qualitative and quantitative data that would indicate how the patient "improve[d]." We believe

our study is somewhat similar to this in the sense that it utilized a survey, however the prospective data that we obtained and larger sample size make the results of a more robust contribution to the current literature.

Lastly, the study "Ketamine as Rescue Treatment for Difficult-to-Sedate Severe Acute Behavioral Disturbance in the Emergency Department," by Isbister et al. (2015) examined Ketamine as a rescue agent in patients with violent and agitated delirium after treatment failure. The initial pharmacologic treatment was Droperidol, a typical antipsychotic, and in a small number of cases various benzodiazepines were utilized. In 41% of the patients, the behavior was severe enough and required police assistance to protect emergency department and EMS staff from the patient as well as the patient from harming themselves. The ketamine was successful at sedation in all cases; however, repeat dosing was required in patients who received an initial dose less than 200mg IM. Unfortuantely, do to variability in the answers to the dosing question, we were not able to further substantiate this as the dosing was inconsistently reported between total dose and mg/kg. This study by Isbister et al. recommends dosing greater than 200mg with a range of 4-6mg/kg. The only adverse outcome in this study was vomiting in two patients and a pulse oximetry of 90% in one patient who responded immediately with supplemental oxygen. All protective airway reflexes are maintained with ketamine and airway compromise was not reported in any cases post-ketamine administration. The fact that we had 8 episodes of airway compromise on a lower dosing regimen (1-2mg/kg IV or 5mg/kg IM), call the safety profile into question more so than may be first thought after reading their article.

The gap in the literature failed to integrate the unique aspect of whether or not the paramedic who administered the ketamine observed that the patient did "improve" based on specific and measurable variables that are routinely recorded on the EMS run sheet by an educated paramedic's assessment. Additionally, an evaluation of a percentage of patients, with or without untoward affects, who were transferred was not thoroughly conducted. Due to the fact that there has been an increasing incidence of "undetermined cause of death" in patients who have been restrained physically while in-custody and that the diagnosis of Excited Delirium

Syndrome is one of exclusion during a port mortem assessment, more efforts need to be aimed at reducing the likelihood in patients who present with signs and symptoms of Excited Delirium Syndrome from avoidable morbidity and possibly death (Gerold, 2015). Furthermore, additional research and evidence is needed to further define ketamine as a first line agent in the prehospital setting to safely sedate and transport other patient populations (elderly, post-traumatic brain injury, among many others) with agitated and violent behavior who may not have ExDS in the differential diagnosis, but do need urgent sedation or medical management to mitigate other suboptimal or adverse outcomes prior to arrival at the facility assuming care. Our data does provide more support for the use and safety profile of ketamine; however, with the above-mentioned limitations that were discussed we don't think that with certainty it can be declared to be of minimal risk and that the administering provider should remain vigilant for complications.

Future Directions

A larger sample size needs to be assessed preferably in a prospective fashion with the ability to follow-up on patients after hospital disposition has been determined. It is curious how many of the patients who receive ketamine are truly suffering from an excited delirium as well as how many may have an untoward reaction after care has been transferred from the paramedics. It would also be beneficial to know what the final diagnosis of a patient was who may have appeared to have an excited delirium syndrome and if ketamine is an agent that would be beneficial in more populations.

Conclusion

Ketamine is an effective sedative in 92.73% of adult patients presenting with agitated delirium; however, a rapid onset of sedation should make the provider suspicious for impending respiratory failure. Additionally, prehospital providers found ketamine to be more effective at sedation and 89.86% prefer it's use over midazolam. More research needs to be done to collect to support whether or not ketamine has an increased risk for complications during sedation, specifically airway compromise and the ability to predict who may need advanced airway support and if onset of action truly predicts impending respiratory failure.

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