2020

Prehospital use of ketamine for rapid sedation of the acutely agitated patient

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

PREHOSPITAL USE OF KETAMINE FOR RAPID SEDATION OF THE ACUTELY AGITATED PATIENT

by

DAVID CORRELL

B.S., Trinity College, 2013

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2020

Approved by

First Reader _____

John Weinstein, M.S., Ph.D.
Assistant Professor of Medicine

Second Reader _____

Adam Broughton, M.S., PA-C.
Assistant Professor of Medicine

ACKNOWLEDGMENTS

I would like to thank my parents, Nora and Peter, and my partner, Nikki. Without their love and support I would not have been able to get to where I am today, let alone complete this body of work. I would also like to thank my readers and advisors, Dr. John Weinstein and Professor Adam Broughton for their expert advice and guidance during this process.

PREHOSPITAL USE OF KETAMINE FOR RAPID SEDATION OF THE ACUTELY AGITATED PATIENT

DAVID CORRELL

ABSTRACT

Agitated patients are common in the prehospital environment and pose a significant danger to themselves, the public, law enforcement and prehospital medical providers. Pharmacologic and non-pharmacologic options exist for managing agitation in the prehospital setting. Severe agitation is best managed with pharmacologic methods, but the optimal drug or drug combination is unclear. Intramuscular (IM) ketamine has been shown to be very effective at obtaining fast and safe control of severely agitated patient. However, current research on this subject is limited to retrospective studies and case series. This proposal is a 2 year, single-center, double-blind randomized controlled trial which will measure the potential superiority of ketamine compared to a commonly used standard-of-care medication (IM haloperidol) for the rapid sedation of acutely agitated patients in the prehospital environment. It will be the first randomized, controlled, double blind study investigating the use of ketamine compared to haloperidol in the prehospital setting for agitation and will impact prehospital protocols for the treatment and management of agitation. It will potentially aid in the future reduction of harm to medical and law enforcement personnel by violent patients as well as decrease morbidity and mortality to the acutely agitated patients.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AMSS…….…… Altered Mental Status Score

BZD…….Benzodiazepine(s)

CNS……..….. Central Nervous System

ED……... Emergency Department

EEG…….... Electroencephalogram

EMS……..……..…Emergency Medical Services

EMT……..……. Emergency Medical Technician

FDA……. Food and Drug Administration

GABA……...…… *y*-aminobutyric acid

GCS...……..…… Glasgow Coma Scale

IM……..…… Intramuscular(ly)

IN…… Intranasal(ly)

IRB…… Institutional Review Board

IV……...…… Intravascular(ly)

NMDA…….….. *N*-methyl-*D*-aspartate

PCP…….….Phencyclidine

PO……. Oral(ly)

RASS…….….. Richmond Agitation Sedation Scale

INTRODUCTION

Background

Patient agitation in the prehospital environment is a common occurrence. These individuals pose a threat to themselves, the public, law enforcement and prehospital medical providers tasked with safely controlling and treating these potentially dangerous patients. Various methods can and have been used when dealing with these patients, from non-pharmacological interventions such as verbal de-escalation or physical restraint to pharmacologic interventions, of which there are many. The choice of method used can have significant impacts on patient, provider and bystander safety and patient morbidity and mortality. Additionally, the manner of de-escalation, type of restraint used and/or pharmacologic agent employed varies not only according to situation but also resource availability, provider preference and education and local culture/protocols.

Agitation presents on a spectrum from mild to severe and no two patients present similarly. As such, it is difficult to know what the optimal way of treating an agitated patient is and it often comes down to provider preference. Unfortunately, very little time is spent during medical education on the treatment of agitation which means that most providers will base their treatment approach simply on their prior training and familiarity with certain drugs or techniques and not necessarily best medical practices. Agitation can be caused by a number of underlying etiologies - neurologic, cardiopulmonary, metabolic, substance-related, or psychiatric. Since an agitated patient presents a significant potential harm to themselves or others, de-escalation by the safest means necessary and available is of the utmost importance.

Statement of the Problem

It is vital for the safety of the patient, first responders and bystanders to gain control of agitated patients in a timely, safe, and appropriate manner. The optimal method for chemical sedation of the agitated prehospital patient is hotly debated and current literature fails to provide a general consensus.

Hypothesis

Due to its favorable hemodynamic profile, lack of respiratory depression, tendency to preserve respiratory reflexes and rapid onset of action when given IM, ketamine is more effective than IM haloperidol for gaining rapid control of the acutely agitated patient in the prehospital environment with a tolerable side effect profile.

Objectives and specific aims

With its unique pharmacodynamic properties in mind the objective of this study is to determine if ketamine is superior to haloperidol for use by prehospital personnel for the primary treatment of the undifferentiated agitated patient. Specific aims include:

- To review the history and pharmacology of ketamine and it's past, present and future uses
- To review the current treatment options for undifferentiated agitation in the prehospital environment
- To compare the effectiveness of ketamine to current, more commonly used treatment options focusing on time to effective sedation and side effects.

- To review the side effect and safety profile of ketamine in conjunction with more commonly used treatment options in an effort to determine if it is an optimal agent for the first-line treatment of undifferentiated prehospital agitation

REVIEW OF THE LITERATURE

Overview

Acutely agitated patients are a common presentation in the prehospital and emergency department (ED) environments. The definition of agitation is not readily agreed upon in the current literature. In addition, agitation itself presents on a spectrum ranging from mild agitation, requiring no pharmacologic intervention, to the severe agitation which must be treated as a medical emergency. Gaining control of an acutely agitated or violent patient is paramount for the safety of medical providers, the patient and bystanders. Many pharmacologic options exist for chemical sedation. The current literature investigating the optimal agent is shrouded with conflicting evidence, experience-based opinion and results open to interpretation.[1] Research has shown that ketamine is an effective and safe drug for use in the prehospital setting and ED for patients presenting with agitation and violent behavior.[2] The majority of studies that have been conducted on this topic are either retrospective chart reviews, case series or prospective studies in the ED, which have limitations due to the nature of the study design (bias, confounders, lack of control group for comparison).[1] The methods, results and limitations of these studies with be discussed below.

Ketamine

Ketamine, a derivative of phencyclidine (colloquially known as the drug of abuse PCP), is a potent analgesic, dissociative anesthetic and sedative-hypnotic which has recently regained popularity in the medical community. It was first synthesized in 1962 by Calvin Stevens, a professor of organic chemistry at Wayne State University (Detroit, Michigan) and chemical consultant of the Parke-Davis and Company laboratories (Detroit, Michigan).[3] Ketamine was first approved by the Food and Drug Administration (FDA) in 1970 as a surgical anesthetic and was used extensively during the Vietnam war for surgery and pain control in wounded soldiers due to its favorable side effect profile.[4] During this time ketamine started to be used as a drug of abuse and was labeled a Schedule III substance by the Drug Enforcement Administration in 1973.[4] Ketamine continues to have a role in veterinary medicine for surgical procedures and sedation, specifically those that do not require skeletal muscle relaxation.[5]

Mechanism of Action

Ketamine acts on many different receptors in the body, which largely accounts for its unique pharmacologic profile. Ketamine acts as a non-competitive antagonist to the *N*-methyl-*D*-aspartate (NMDA) receptor and it is thought that this mediates its use as a sedative. The NMDA receptor is the normal target of glutamate, one of the brains excitatory transmitters. Most commonly used anesthetics, such as benzodiazepines (BZD), propofol and inhaled volatile gases (e.g. sevoflurane), enhance the effects of *y*-aminobutyric acid (GABA), an inhibitory neurotransmitter. Apart from NMDA receptor antagonism, ketamine also directly affects the following receptors, channels and systems:

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, hyperpolarization-activated cyclic nucleotide channels (HCN1), nicotinic acetylcholine ion channels, delta and mu-opioid agonist, opioid potentiation, nitric oxide-cyclic guanosine monophosphate system, metabotropic glutamate receptors, dopamine and noradrenaline neuromodulation and L-type calcium channels.[6] The multitude of mechanisms working in concert is hypothesized to be responsible for ketamine's unique and varied physiologic effects.

Chemical Structure

Ketamine chemical name is (+/-) 2-(2-chlorophenyl)-2-(methyl-amino)cyclohexanone. Ketamine has a molecular formula of $C_{13}H_{16}ClNO$, a molecular weight of 237.7 g/mol and a pKA of 7.5.[7] Ketamine is a chiral molecule. The S(+)-isomer is a 3-4 time more potent anesthetic than the R(-) enantiomer.[8]

Pharmacokinetics

Ketamine is both water and lipid soluble allowing it to be delivered by a large variety of routes. It has a bioavailability of 100% when administered intravenously (IV), 93% IM, 25-50% intranasally (IN), and 17% orally (PO). The onset of action is seconds with IV administration, 1-5 minutes IM, 5-10 minutes IN, and 15-20 PO. Duration of effect is approximately 30-45 minutes IV/IM, 45-60 minutes IN, and 1-2 hours PO.[8]

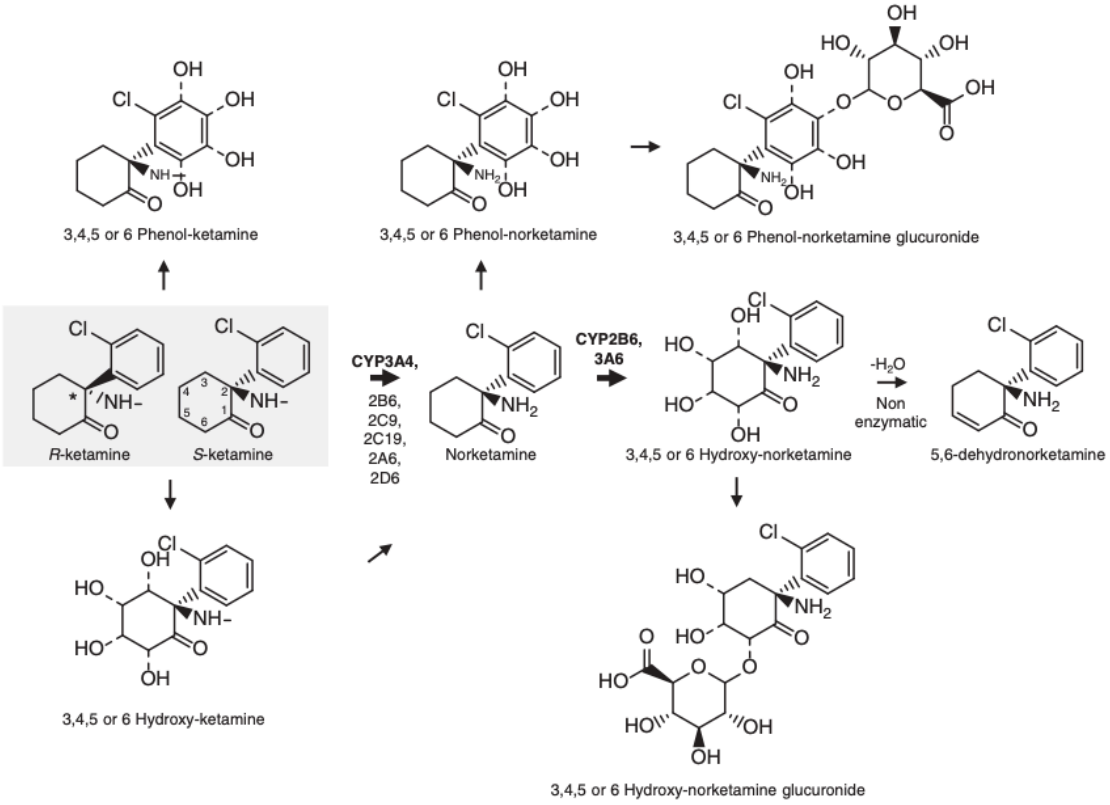
Distribution

Ketamine has a 12% binding to plasma protein[8]. Due to its high lipophilicity and low protein binding, it rapidly distributes across the blood-brain barrier into the central nervous system, where its concentrations can be 4-5 times that of plasma.[9] These characteristics allow ketamine to produce a large volume of distribution (3-5 L/kg).[10]

Metabolism

Ketamine is almost exclusively hepatically cleared with the major metabolic pathways being *N*-demethylation to norketamine, mainly via the CYP3A4 pathway with minor contributions of the CYP2B6 and CYP2C9 isoforms.[10,11] Norketamine retains some of the psychoactive and anesthetic properties of ketamine, although at approximately one third the potency, which helps to explain the continuation of therapeutic effects even when ketamine plasma levels are low.[10,12] Oral ketamine undergoes significant first-pass metabolism to norketamine. The elimination half-life of ketamine is approximately 2-4 hrs and is similar in adults and children, although children produce more norketamine which necessitates higher infusion rates.[10,13] 6-hydroxyketamine, an inactive metabolite, is produced via norketamine hydroxylation.[11] Dehydronorketamine is produced via norketamine dehydrogenation.[14] See Figure 1 for the metabolism of ketamine.

Figure 1: Metabolism of Ketamine



From Dinis-Oliveira, 2017[10]

Excretion

Ketamine and its metabolites are excreted in urine with 80% being conjugates of hydroxylated/glucuronidated metabolites and 16% being dehydronorketamine.[10,11] Approximately 2% of ketamine and 2% of norketamine are excreted unchanged in urine, the former being detectable up to three days after administration. Length of detection seems to be impacted with chronicity of use.[8]

Pharmacodynamics

Central Nervous System (CNS)

Ketamine depresses the sensory association areas of the cortex, components of the limbic system, and the thalamus, which results in anesthesia, analgesia, suppression of fear and anxiety, and amnesia.[15] On EEG, there is a predominance of theta waves and abolition of alpha waves when ketamine is administered at induction doses.[16] No increase in intracranial pressure is seen with administration of ketamine at 5 mg/kg IV.[17,18]

Cardiovascular

Modest increases in heart rate and blood pressure occur with ketamine administration. This effect is mediated through central catecholamine reuptake inhibition. Ketamine is relatively contraindicated in patients with severe coronary atherosclerotic disease due to the theoretical risk of myocardial ischemia.[19,20].

Respiratory

There is no significant respiratory depression produced with ketamine administration, which is an almost universal side effect of most commonly used anesthetics.[21] Since skeletal muscle tone is maintained during ketamine anesthesia changes in functional residual capacity do not occur.[21] Upper airway skeletal muscle tone and pharyngeal reflexes are maintained.[19,22] Laryngeal reflexes are depressed with ketamine administration resulting in the possibility of aspiration, however, this is rare.[22]

Other

Ketamine increases muscle tone, blood glucose, plasma cortisol and prolactin.[23]

Side Effects

Emergence reaction

Emergence reactions occur in up to half of patients administered ketamine.[24] These reactions typically occur as a patient is recovering from sedation and include vivid dreaming, agitation, hallucination and delirium, closely mimicking both the positive and negative symptoms of schizophrenia.[19,24] Treatment of emergence reactions is easily achieved through administration of a BZD, providing a safe and quiet recovery area, and with provider reassurance.[19] Premedication with a variety of medications can reduce the incidence of emergence reactions with midazolam being the most well studied and efficacious.[25] However, this approach does have a higher incidence of respiratory depression and time to recovery of sedation.[19] Emergence reactions are less common in elderly and pediatric patients.[26]

Cardiovascular

Modest increases in heart rate and blood pressure are usually transient and have no negative clinical result.[19] However, ketamine is relatively contraindicated in patients with severe coronary atherosclerotic disease due to theoretical risk of myocardial ischemia.[19] These cardiovascular effects can be mitigated through the use of sympatholytics.[19]

Laryngospasm

While rare, laryngospasm can occur after ketamine administration. It is more common in infants.[27] A meta-analysis of 8,282 children that received ketamine sedation in the emergency department found the incidence of laryngospasm to be 0.3%.[28] Ketamine induced laryngospasm is usually transient and responsive to bag-valve mask ventilation and airway maneuvers.[29]

Respiratory depression/Apnea

Respiratory depression is a relatively rare side effect of ketamine and is often seen shortly after rapid IV administration, overdose or in the setting of coadministration of other anesthetics.[19,30] A meta-analysis of 8,282 children who received ketamine sedation in the emergency department found the incidence of apnea to be 0.8%.[28]

Hypersalivation

Hypersalivation is a relatively common side effect (up to 30% in some studies), which is easily treated with antisialagogues such as atropine or scopolamine.[31] A clinical trial investigating the comparative effectiveness of atropine and glycopyrrolate for ketamine-induced hypersalivation during minor surgical procedures was underway at the time of this writing.[32]

Other

Vomiting occurs in 5-15% of patients and usually coincides with emergence from anesthesia.[19,33] Nystagmus and mild pupillary dilation can occur.[16] A rash on the upper torso occurs in 5-20% of patients given ketamine shortly after administration and usually subsides quickly, requiring no intervention.[19] Purposeless movements and, less commonly, hypertonus can occur.[33]

Routes of administration

Ketamine can be administered IV, IO, IM, IN, PO, subcutaneously, sublingually, intrathecally or rectally.[30]

Dosing

Dosing varies based on the desired pharmacologic effect and those dosages further vary depending on local hospital or EMS regulations, as well as provider preference. In general, the dissociative anesthetic dose of 4-6 mg/kg IM or 1-2 mg/kg IV is used for procedural sedation, as it produces a trance-like cataplectic state while allowing the patient to maintain their own heart rate, blood pressure and breathing. At a lower dose of 0.15-0.30 mg/kg IV or 0.5-1 mg/kg IN, ketamine has more purely analgesic properties.[30] There is no suggested renal or hepatic impairment dosing adjustments recommended by the manufacturer.[30]

Manufacturing Information

Ketamine is available in the United States as Ketalar (brand name) or generic and is sold in injectable solutions of: 10 mg/mL (20 mL), 50 mg/mL (10 mL), and 100 mg/mL (5 mL, 10 mL-generic only).[20]

Current Uses

Ketamine is commonly used for agitated patients and will be discussed at length in later sections. While there is no officially agreed upon dose for agitated patients, the most commonly used dose is 4-6 mg/kg IM or 1-2 kg/mg IV.[30] Ketamine is also used for anesthesia (induction, maintenance and local), procedural sedation, acute pain, chronic pain, asthma, status epilepticus, depression and inflammation. While fascinating, an in-depth discussion of these uses are outside the scope of this research proposal.

Agitation and Excited Delirium

Acute agitation is a common symptom that can be the result of a number of medical or psychiatric disorders. Excited delirium is a subtype of agitation characterized by mental status changes, psychomotor agitation, increased strength, hyperthermia and, often, sudden death attributed to cardiopulmonary arrest.[34,35] Excited delirium carries a high risk of mortality with as many as 2/3 of patients dying in the prehospital environment.[36] The etiology of agitation is not well understood but likely involves homeostatic disruption of dopamine, norepinephrine, serotonin and GABA.[37] Drug and alcohol intoxication is noted in up to 80% of patients presenting with acute undifferentiated agitation.[38] There

are five features of clinically significant agitation, as defined by a psychiatric consensus group in an attempt to clarify the variability of the condition in the current literature (Table 1).[39]

Table 1: Five Features of Clinically Significant Agitation[39]

1. Abnormal and excessive verbal behavior such as shouting, cursing, threatening, or screaming
2. Abnormal or excessive physically aggressive behavior such as pushing, shoving, actively resisting care, repeatedly attempting to elope, or excessive threatening gestures
3. Heightened arousal
4. Symptoms cause clinically significant disruption of patient's functioning
5. Abnormal excessive or purposeless motor behavior

Agitation is a positive predictor of potential aggressive or violent behavior.[40] Organic causes of agitation include brain tumors, encephalitis, cerebrovascular accidents, traumatic brain injuries, electrolyte, hormone or vitamin imbalances, infections or intoxication.[34,41] Inorganic causes of agitation include psychiatric disorders, such as schizophrenia or bipolar, and neurocognitive disorders, such as dementia.[34,41] Agitation can lead to violence and harm to the patient, caregivers and bystanders.[28] This danger necessitates prompt recognition and intervention to reduce harm. This is especially true in the prehospital environment. Data from the Department of Labor Bureau of Labor

Statistics found that emergency medical technicians (EMT) and paramedics in the United states are at twice the risk of on the job assault compared to all other occupations and patients are often the perpetrators of assault against prehospital medical providers.[42,43] It is estimated that one-third of occupational injuries sustained by EMTs are patient related.[43] The consensus statement of the American Association of Emergency Psychiatry Project BETA Psychopharmacology Workgroup[39] focuses on three main goals surrounding the management of acute agitation or excited delirium in the prehospital setting, summarized by Linder et al: early recognition and treatment of the underlying etiology; rapid control of the behavior; and prevention of harm to both the patient and EMT personnel.[34]

Interventions for the agitated patient

While non-pharmacologic methods, such as verbal de-escalation or environmental modification, are the optimal first intervention, they are not always successful and, thus, physical or pharmacological restraint becomes a necessity. Additionally, sometimes the severity of the situation necessitates more rapid de-escalation and, therefore, time-consuming non-pharmacologic interventions are not suitable and put the patient and provider at increased risk. Seclusion of the acutely agitated patient is a controversial but commonly used practice in the ED but is not possible in the prehospital environment.[41] Mechanical restraints are an option that should be considered when other treatment options have failed, as their administration poses a risk to both the patient and caregivers. Their continued use poses additional danger to the patient who can still cause themselves

harm.[41] Mechanical restraint can lead to injury of extremities, stress cardiomyopathy, rhabdomyolysis from constant straining, positional asphyxia, exacerbation of acidosis and sudden death.[35,44]

When the situation dictates, pharmacologic management of the acutely agitated patient is warranted. The properties of the ideal medication for the acute management of agitation are outlined in Table 2, adapted from Ng et al.[45]

Table 2: Theoretical Properties of the Ideal Medication for the Acute Management of Agitation

- Easy preparation by staff
- Non-traumatic, non-painful administration
- No requirement for restraint for administration
- Possibility of self-administration
- Rapid onset of action
- Little interpatient variability with regards to pharmacokinetics/dynamics
- Offset sufficiently slow for transport of patient to appropriate services
- Provides tranquilization without excessive sedation so as to not interfere with patient interaction, diagnosis, and selection of additional therapy
- Low risk for significant adverse reactions and drug interactions

As such a medication does not exist, emergency practitioners must use clinical judgment when choosing which medication from their formulary to use for the acutely agitated patient. Common medication options include BZDs (midazolam, lorazepam and

diazepam), typical antipsychotics (haloperidol, droperidol) and atypical antipsychotics (aripiprazole, olanzapine, risperidone, ziprasidone). Their strengths and drawbacks are discussed below.

Common BZDs used to chemically restrain agitated and violent patients include midazolam, diazepam and lorazepam. BZDs are one of the most commonly used drugs for sedation and are recommended for agitated patients undergoing drug intoxication or withdrawal.[46] Midazolam is the most commonly used with a rapid time of onset of minutes and a relative short half-life of 1.5-2.5 hours.[47] Common side effects include respiratory depression, excessive somnolence and oxygen desaturation which often leads to the need for airway interventions.[46,48]

Typical antipsychotics, most notably butyrophenones (haloperidol and droperidol), have been a common first-line treatment for agitated and violent patients, especially in those with known psychiatric illness.[46] Pairing antipsychotics with BZDs and/or diphenhydramine has been shown to result in more rapid sedation of the patient and is a common ED practice.[49] However, these drugs are known to have slow onset of action when administered IM and lead to QTc prolongation, which increases the risk of torsade's de pointes, a potentially fatal arrythmia. Droperidol carries a black box warning from the FDA for this and as such has fallen out of favor in recent years.[44] Haloperidol carries the same warning but is still commonly used for agitation. Other side effects include extrapyramidal symptoms (dystonia, akathisia, parkinsonism, tardive dyskinesia) and neuroleptic malignant syndrome.[50] It should be noted that diphenhydramine can help

reduce some extrapyramidal symptoms from administration of antipsychotics but it can also result in some QTc prolongation.

Atypical antipsychotics (aripiprazole, olanzapine, risperidone, ziprasidone) are known to cause QTc prolongation (ziprasidone having the most significant and dose-dependent effect), albeit less than typical antipsychotics.[51] These drugs are also associated with fewer extrapyramidal side effects.[46] Their use for agitation is still in its infancy in comparison to typical antipsychotics and BZDs and largely restricted to the emergency department.

Existing research

Prehospital use of ketamine for agitation by EMS personnel

Burnett et al conducted a retrospective chart review study in 2012 investigating the effect that prehospital ketamine administration had on a patients ED course. The study included 13 patients who were chemically restrained by paramedics who had received formal training on excited delirium using ketamine at an IM dose of 5 mg/kg. Weights were estimated in the field. All EMS and 12/13 ED records were reviewed as part of the study. Sedation was quantified using the Richmond Agitation Sedation Scale (RASS), a scale used by many hospitals to quantify levels of sedation and agitation ranging from -5 (unarousable) to +4 (combative). All patients treated reached a RASS score between -5 and -2. Peak sedation occurred in <5 minutes for 11/13 patients and in <20 minutes for the remaining 2 patients. Intubation occurred in two patients who developed hypoxia. A third patient who developed hypoxia was successfully treated with

a jaw thrust maneuver. Indications for intubation were recurrent laryngospasm (n=1) and intracranial bleeding (n=1), the latter of which was not attributed to ketamine administration. Adverse effects included hypoxia, laryngospasm, and hypersalivations. Additionally, emergence reactions occurred in 30% of non-intubated patients and all were treated with low dose BZDs.[52]

Ho et al, 2012 reported on two incidents where ketamine was used by prehospital paramedics for the pharmacologic sedation of two intoxicated patients presenting with excited delirium. While both patients were intubated it was reportedly due to severe metabolic acidosis and not respiratory compromise. Both patients were reported to have good hospital outcomes without complications. No adverse effects of ketamine were reported.[53]

Scheppke et al performed a retrospective study in which paramedic run sheets were screened from January 1, 2011 to May 1, 2014 for cases where their prehospital ketamine protocol was used for violent or aggressive behavior which identified 52 patients. Patients were administered ketamine at 4 mg/kg IM (max 400 mg). Once adequate sedation and control of the patient was achieved IV access was attempted and midazolam (2-2.5 mg) was given IV/IM for emergence reaction prophylaxis. The primary endpoint was adequate sedation with ketamine of sufficient duration to effectively treat and transport patients to definitive care. Untoward hemodynamic effects were defined as any resuscitation needed for a systolic blood pressure of <90 mm Hg. Untoward respiratory effects were defined as any intervention requiring positive pressure ventilation. Sufficient sedation was achieved at a dose of 4 mg/kg IM in 50/52 (96% of

cases). In these 50/52 patients, adequate sedation was achieved in average of just over 2 minutes and adequate sedation was maintained throughout transport (average transport time of 19 minutes from time of injection). Respiratory depression was reported in 3 cases, 2 of which required intubation and 1 of which required positive pressure ventilation. In all three cases, the patient had already received IV midazolam. Almost half of the patients received IV/IM midazolam with or shortly after ketamine administration. A limitation to this study was that the patients were not followed after transfer to the ED so adverse effects in the ED and beyond were not available for analysis. Another limitation noted by the authors was that there was a significant amount of missing data (such as recorded temperatures) on the run sheets filled out by paramedics, which could have played a role in their analysis. However, the authors note that there was likely not any significant adverse events that were missed, as anything significant would have required additional interventions which would be less likely to be missed in documentation.[2]

Burnett and colleagues published a retrospective chart review in 2015 investigating the impact of prehospital ketamine administration by an urban fire-based EMS service on intubation and hospital admission. Patients who received ketamine for chemical restraint and were transported to a single level 1 trauma center (N=49) were included in the study analysis. Mean ketamine dosing was 5.26 +/- 1.65 mg/kg with a range of 2.25-9.42 mg/kg. While no patients were intubated in the prehospital environment, 14/49 were intubated in the hospital. The intubated patients received a statistically higher amount of ketamine compared to the unintubated patients (6.16 +/-

1.62 v. 4.90 +/- 1.54 mg/kg, p= .02). Reasons for intubation were failure to protect airway (7/14), recurrent agitation with need for additional sedation (2/14), to facilitate emergent lumbar puncture (1/14), hypoxia (1/14), laryngospasm (1/14) and unknown (2/14). Among patients admitted to the hospital (71%; 35/49), most were for medical, rather than psychiatric, diagnoses (28 v. 7). The ketamine dose for those patients admitted to the hospital compared to those discharged from the ED did not reach clinical significance. Alcohol intoxication was present in the discharge diagnoses of 61% (17/28) admitted to a medical bed and 57% (8/14) who were intubated. The authors note that their study suffered from a referral bias as they only included data from patients transferred to the only level 1 trauma center in the area, which could have falsely elevated rates of intubation and hospital admission. Another limitation is that the study did not control for potential confounders such as alcohol intoxications, ingestions and baseline morbidities. It should also be noted that the authors were unable to objectively determine the causality of prehospital ketamine administration on the decision to admit as the ED provider documentation for admission was often vague and referred to ongoing workup for altered mental status. Finally, the authors astutely noted that their association between ketamine dose and intubation and hospital admission did not establish causality.[54]

Burnett and colleagues published another retrospective chart review study in 2015 exploring whether ketamine administration was associated with significant increase in on-scene time for an agitated patient compared to haloperidol. The study was appropriately powered with 110 patients included; half received ketamine and the other half received haloperidol +/- BZD and/or diphenhydramine. A statistically significant

increased time on-scene was determined to be ≥5 minutes, as the authors felt that this represented a clinically significant difference in on-scene time. No clinically significant difference in on-scene time was found between groups. Limitations apart from this being a retrospective chart review analysis included the study being limited to a single EMS service in a large metropolitan area with short transport time to definitive care, which reduced the generalizability of the study. Additionally, the data acquired from the electronic patient care reports filled out by paramedics was not controlled for accuracy, which leaves room for reporting error.[55]

Keseg et al, in 2015, performed a retrospective cohort chart review on the use of ketamine in a metropolitan firefighter-based EMS system over a two-year period. The intent was to provide a descriptive analysis of the prehospital providers' experience using ketamine for acute agitation under the hypothesis that it would improve the patient's condition, be effective in sedating the patient and not result in endotracheal intubation. To avoid undue cost and educational burdens, only the EMS supervisor vehicle was stocked with ketamine and only the EMS supervisor was able to administer ketamine. Ketamine was administered at a dose of 4 mg/kg IM or 2 mg/kg IV. Thirty-five patients were included in the analysis. The primary outcome was the percentage of patients noted to have improved, while the secondary outcomes were the effectiveness of sedation (defined as proportion of patients needing additional chemical sedation or the use of significant force (conducted electrical weapons, lachrymatory agents or physical force)) and the performance of endotracheal intubation. One limitation with this study design was that only the EMS supervisor could administer ketamine and the presence or absence

of the supervisor likely impacted the decision to administer ketamine. Another limitation was that the improvement in patient condition was simply based on the paramedic provider subjectively marking 'improved' or 'not improved' in the prehospital patient care report and not based of any standardized assessment or objective data. This also had the potential to introduce significant reporting bias. A further limitation was that investigator blinding and interrater reliability was not performed, although the authors do note that all extracted variables were present as discrete data points and, thus, did not require interpretation by an abstractor[56].

Cole and colleagues in 2016 published a prospective open-label observational study of patients treated for severe agitation in the prehospital environment and transported to an urban Level 1 trauma center safety net hospital. The primary study objective was to determine whether haloperidol (10 mg IM) or ketamine (5mg/kg IM) was superior for the treatment of severe prehospital acute undifferentiated agitation. Secondary outcome objectives included need for redosing in the prehospital environment, rate of adverse side effects and rates of intubation. Severe agitation was defined as an Altered Mental Status Score (AMSS) of +2 or +3. Patients with a score of +4 were excluded as the authors had over 10 years of experience successfully treating profoundly agitated patients with ketamine and the authors deemed it unethical and unwise to withhold ketamine from the most profoundly agitated patients at any time for both patient and caregiver safety. The AMSS is a 9 point (+4 to -4) scale that determines a patient's agitation (+1 to +4) or sedation (-1 to -4) and includes 4 descriptors (responsiveness, speech, facial expression and eyes; Table 3)[57]. AMSS scores were recorded every 5

minutes until adequate sedation was achieved (AMSS +1). To avoid seasonal bias, the standard operating procedures for patients requiring chemical sedation included haloperidol 10 mg IM for the first 3 months, ketamine 5 mg/kg IM for the next 6 months and then haloperidol 10 mg IM for the remaining 3 months. Time to adequate sedation was recorded with a stopwatch. Research associates trained in a similar manner to paramedics continued assessment of the patient using the AMSS every 30 minutes until ED discharge or hospital admission. Airway and sedation problems (hypersalivation, emergence reaction, vomiting, laryngospasm, akathisia, dystonia and death) were assessed by research associates in real time. Time to adequate sedation was significantly lower ($p < 0.0001$) in the ketamine group (median 5 minutes, rang 0,4-23) compared to the haloperidol group (median 17 minutes, range 2-84). Patients who received ketamine had a significantly ($p<0.0001$) higher rate of being adequately sedated (95%) compared to the patients who received haloperidol (65%). There were significantly more complications ($p < 0.0001$, 49% v 5%) and intubations ($p < 0.0001$, 39% v 4%) in the ketamine group compared to those receiving haloperidol. All intubations occurred in the ED. The authors noted that the intubation rate in this study was much higher than in most similar studies with the most common reason being that the ED provider felt that the patient was not protecting their airway. The authors postulated that this was likely due to ED provider discomfort with the dissociated patient or that they misapplied the commonly used axiom “intubation for a Glasgow Coma Scale of 8,” since a patient dissociated with ketamine would have a GCS of 3. Additionally, the authors pointed out that the procedural sedation literature has an apnea rate of 0.8% at similar IM ketamine

doses, further supporting the aforementioned hypothesis. One limitation was that prehospital and ED caregivers were unblinded to which medication was administered to the patient. Another limitation was the lack of randomization and blinding. This was thought to contribute to the reduction in number of patients enrolled during the ketamine arm of the study as the authors found some evidence although they did not elaborate on what the evidence was) that paramedics were less likely to sedate patients when ketamine was the only available sedative.[58].

Table 3: Altered Mental Status Scale

Score	Responsiveness	Speech	Facial expression	Eyes
4	Combative, violent, out ofcontrol	Loud outbursts	Agitated	Normal
3	Very anxious, agitated, mild physical element of violence	Loud outbursts	Agitated	Normal
2	Anxious, agitated	Loud outbursts	Normal	Normal
1	Anxious, restless	Normal	Normal	Normal
0	Responds easily to name, speaks in normal tone	Normal	Normal	Clear, no ptosis
-1	Lethargic response to name	Mild slowing and thickening	Mild relaxation	Glazed or mild ptosis < 1/2 eye
-2	Responds only if name is called loudly	Slurring or prominent slowing	Marked relaxation	Glazed and marked ptosis> 1/2 eye
-3	Responds only after mild prodding	Few recognizable words	Marked relaxation, slacked jaw	Glazed and marked ptosis > 1/2 eye
-4	Doesn't respond to mild prodding or shaking	Few recognizable words	Marked relaxation, slacked jaw	Glazed and marked ptosis > 1/2 eye

Olives and colleagues published a retrospective chart review study in 2016 describing intubation rates in agitated patients treated with prehospital ketamine and transported to an urban Level 1 trauma center over a 40 month period. Of the 135 patients included in the study, 85 were intubated (63%), independent of ketamine dose, coadministration of haloperidol or midazolam, or age. Male gender and late-night arrival (2300-0700) were significantly associated with intubation and persisted in adjusted

analyses. Two patients sustained cardiac arrest after ketamine administration but the cause of death was determined to be related to ingestion (citalopram, amphetamine, clonidine) and hypernatremia combined with medical comorbidities (seizure disorder with subtherapeutic anti-epileptic drug levels, atherosclerotic heart disease, hypertension, cardiomegaly and history of substance abuse). The study noted that the definition of the patient population in this study --profoundly agitated -- likely impacted the decision to intubate regardless of the choice of sedative used. The study also found in *post-hoc* analyses a provider dependent practice with respect to airway management of profoundly agitated patients treated with ketamine, especially when resources were limited during overnight shifts. The retrospective, single-center observational nature of this study is one limitation to this study. Specifically, the inability to control for the exact reason of intubation and the nuances behind that decision (eg paramedic report, ED provider familiarity with ketamine and the prehospital provider, anticipated clinical course, and resource availability). Another limitation was that these patients were not followed after their time in the ED and thus length of intubation and morbidity and mortality after ketamine administration for profound agitation could not be analyzed. The authors conclude their article with an important statement about the need for provider discomfort with the dissociated patient and how this likely impacts intubation of patient sedated with ketamine, a common finding in this and many other studies, and must be controlled for before any final conclusions can be drawn about the superiority or lack-thereof of ketamine in regards to prehospital sedation for agitation. [59]

In 2018 Cole et al published a study investigating the effectiveness of ketamine as a primary therapy for prehospital profound agitation in a prospective, observational study. The study enrolled 49 patients with a median age of 29. They defined profound agitation as an AMSS score of +4. The primary outcome measure was time to adequate sedation (AMSS < +1). Secondary outcomes were the need for additional sedatives, intubation frequency, complications associated with ketamine administration and mortality. Mean ketamine dose was 4.9 mg/kg based on weights obtained in the emergency department. Median time to adequate sedation was only 4.2 minutes. Complications included hypersalivation (18%), vomiting (6%) and emergence reaction (2%). One patient died on hospital day 29 from complications from septic shock, which was unlikely to be due to ketamine administration. Intubation occurred in 59% of patients administered IM ketamine. Most patients (82%) were extubated in <24 hrs and nearly all (96%) in <48 hrs. The authors noted that one physician who worked only nights accounted for 36% of these intubations and that 22% of others were from providers with minimal experience with patients sedated with ketamine. Additionally, as previously noted in Cole et al, 2016, the authors postulate that the appearance of a patient sedated with ketamine is similar to a patient with a GCS <8, which is commonly used as a reason to intubate a patient. They also mention that the majority of intubations used 'Airway Unprotected NOS' as the reason for intubation, a catch-all term that provides little information as to the reason the patient needed intubation. Future studies require more specific investigation into exact reasoning for intubation by each provider. The authors argue that intubations after ketamine administration should be viewed as adverse events

because intubation and mechanical ventilation both pose significant risk themselves and the duration of mechanical ventilation for nearly all patients (96%) was short (<48 hrs) and the 1 patient who remained ventilated had multiple chronic medical comorbidities, was in acute renal failure and later died as a result of complications of septic shock, the likely etiology of his profound agitation which led to him being sedated with ketamine. [60]

O'connor et al published a single-center retrospective review study in 2018 on the outcomes of prehospital chemical sedation with ketamine compared to haloperidol and benzodiazepines or physical restraint alone. Of the 214 subjects enrolled in the study, 95 received ketamine, 68 received haloperidol and benzodiazepines and 51 were physically restrained. The intubation rate for patients administered ketamine was higher than those in the other two groups but much lower than other ketamine studies at only 11.6%. Furthermore, there was no difference in ED length of stay or hospital admission rate between either chemical sedation groups. The authors found an increased intubation trend with overnight presentation and with documented co-ingestion. Additionally, as observed in the Cole et al, 2018 study, one physician was responsible for 54.5% of the ketamine intubations. The mean ketamine administration was 3.68 mg/kg, less than other studies which usually used 4-5 mg/kg dosing. This could be the reason for the decreased intubation rate found in this study. The authors postulate that intubations with ketamine sedation are likely multifactorial but are commonly associated with overnight arrival and 'high acuity low resource' situations. This is likely due to provider discomfort with patients sedated with ketamine. It is unclear whether a patient sedated with ketamine has a more precarious airway than one sedated by other means and this deserves further

exploration. Furthermore, the rate of intubation when compared to resource availability in the ED needs to be controlled for when doing these types of analysis. Interestingly, this study found that patients who received ketamine were more likely to require additional ED sedation, which has not been seen in most other studies. This is likely due to the half-life of ketamine being much less than haloperidol or lorazepam, the BZD used in this study. The major limitations of this study were the relatively small sample size and conduction at a single center which could impact the results due to local practice patterns, resource limitations and provider preference. [61]

Mankowitz et al published a systemic review in 2018 of ketamine use for sedation of agitated patients in the ED, prehospital environment and air-medical transport. The most important limitation that they noted in the 18 studies they analyzed in their report was that all studies were observational in nature and most were retrospective. They stress the need for randomized, blinded trials to determine the safety and efficacy of ketamine as compared to other sedatives for agitation.[1]

In summary, ketamine use in the prehospital environment provides fast sedation of agitated patients with a higher side effect profile, although these side effects are typically self-limiting or are easily treated with commonly available medications or interventions. Prehospital use of ketamine is associated with higher rates of endotracheal intubation than other sedatives but the reason for intubation appears to be largely influenced by provider comfort with the dissociated patient and the true need for intubation in many of these patients is questionable as the mean duration of mechanical ventilation for most patients is under 24 hours. It is undeniable that randomized,

controlled trials are required to determine if ketamine is indeed the optimal drug of choice for sedating the acutely agitated patient in the prehospital environment.

METHODS

Study design

This proposal will investigate the efficacy and safety of ketamine compared to haloperidol for the rapid sedation of acutely agitated patients in the prehospital environment in a 24-month double-blind randomized controlled trial. The study will take place at Boston Medical Center, an academic level 1 trauma center in Boston, Massachusetts, USA. It will run from September 2020 to August 2022.

Study population and sampling

Recruitment of participants will occur from the community served by the Boston Emergency Medical Service (EMS), which provides pre-hospital care to 19 neighborhoods within the Greater Boston Area. Boston EMS is the primary emergency medical provider for the city of Boston and responds to approximately 125,000 emergency calls per year[62]. The criteria for selection are outlined in Table 4. Participants will be identified in the field and transported to Boston Medical Center. Since it will be difficult to identify if a patient meets exclusion criteria in the prehospital setting a study coordinator will perform a detailed search of the electronic medical record and communicate with medical providers at Boston Medical Center to determine if the participant meets any exclusion criteria. If it is determined that the participant does meet exclusion criteria, then they will be removed from the study.

Table 4: Inclusion and Exclusion Criteria for Selecting Participants[63,64]

Inclusion Criteria	Exclusion Criteria
• Age 18-65 • AMSS between +2 to +4 • Acute danger to self and/or others	• Women suspected or known to be pregnant or breast feeding • Evidence or history of head trauma within the past 30 days • History of schizophrenia / schizoaffective disorder • Treatment with BZD or neuroleptics within the past 24 hours • Underlying lung conditions (COPD, poorly controlled asthma, interstitial lung disease) • Known active malignancy • Dementia • Intellectual disability • Individuals with a history of cerebrovascular accident • Individuals with severe cardiac decompensation

The estimated sample size will be approximately 120 individuals (60 in each group) This is based upon the trial conducted by Heydari et al in 2018 that looked at the use of ketamine versus haloperidol for short term control of severely agitated patients in the emergency department.[64] The difference in the mean sedation time was 3.69 minutes with a standard deviation of 7.2 minutes. The alpha will be 0.05 and the beta is 0.20. The explanatory variable will be either ketamine or haloperidol use for agitation control. The primary outcome will be time to successful sedation (AMSS $\underline{\leq}$+1), measured in minutes.

Intervention

Participants who meet inclusion criteria will be randomized to either haloperidol (10 mg IM) or ketamine (400 mg IM) groups and immediately assigned a randomized study identification number. Randomization will be done using a randomized block design with varying block sizes. Each arm will contain an equal number of participants. The

randomization schedule will be stored with the study medication. It will be dispensed daily by an EMS supervisor according to the schedule to EMS crews. Matching medication will be stored in the medication storage system in the ED (Pyxis) and will be dispensed accordingly by an ED pharmacist or nurse who is unblinded. The EMS supervisor and ED pharmacist or nurse will not participate in any of the data collection or assessment of study outcomes.[63,65] Unused or partially used study medications will be disposed of according to the manufacturer's recommendations. All study medications will be stored in pre-loaded administration syringes labeled only with the subject ID number and either primary or additional dose to allow for accurate delivery. If additional sedation is required (AMSS >1) a second dose of ½ the initial dose will be administered. Additional doses will be administered in a similar fashion if deemed necessary by prehospital personnel or the supervising provider in the ED. The need for additional doses or for other sedative medication will be recorded by a study research coordinator. All participants will receive routine ED standard of care, including complete blood count, basic metabolic panel, serum ethanol, serum lactate, venous pH, urine toxicology, telemetry, and a full physical exam by the ED supervising provider. All patient providers will be queried on time to adequate sedation (defined as AMSS $\leq$+1). If the patient is admitted or requires a consultant to further their care, the treatment given will be unblinded to those individuals as they will not have any impact on primary data collection or analysis. If it is deemed at any time by any medical provider that remaining blinded to the medication administered could negatively affect the patient's condition unblinding will occur and the patient will be excluded from analysis. To reduce the

chance of resource limitations influencing intubation decisions a dedicated respiratory therapist will be made available to monitor any patient enrolled in the study.

Study variables and measures

Participants will be divided into haloperidol or ketamine groups. The primary outcome will be time to successful sedation (AMSS $\underline{<+}1$). Secondary outcomes include need for additional dosing, intubation frequency, length of mechanical ventilation, complications from medications (extrapyramidal side effects, laryngospasm, hypersalivation, emergence reaction, vomiting), length of hospital stay, cost of hospitalization and mortality.

Recruitment

Participants will be recruited from the community as outlined in the *Study Population and Sampling* section. Consent will be implied as any patient meeting inclusion criteria will require immediate sedation for patient and provider safety. However, if a legal authorized representative is present at the scene they will be queried for consent. If they do not give consent, the patient will be treated with Boston EMS standard of care for undifferentiated agitation and the patient would not be enrolled in the study. If sufficient numbers of patients are not recruited in the 24-month study period, a request for an extension will be submitted to the IRB to allow for adequate subject recruitment.

Data collection

Data collection will begin immediately when a patient is enrolled in the study. Paramedics trained on the administration of the AMSS (Table 3) will record AMSS scores at 0 minutes and every 5 minutes after administration of IM medication until patient care is transferred to the receiving facility or until adequate sedation (as

determined by an AMSS score of $\leq +1$). A stopwatch attached to the medication box will be started at the moment of administration of the study drug to ensure proper timing, as performed by Cole et al.[60,66] If adequate sedation is not achieved by the time of transfer to the receiving facility, then a blinded nurse or research coordinator will continue to document AMSS scores until adequate sedation is achieved. The stopwatch will be transferred to the blinded nurse or research coordinator in this case. Blood pressure will be monitored every five minutes for no less than the first 60 minutes after medication administration and will continue as long as is deemed necessary by the primary patient provider. Continuous capnography, pulse oximetry, respiratory and pulse rate will be obtained and recorded at similar intervals to blood pressure. Adverse events, rates of intubation, need for redosing and length of hospital stay will be obtained from the prehospital and hospital EMR. Demographic information such as age, sex, history of psychiatric illness, history of trauma, vital signs and toxicology results will also be obtained from the hospital EMR. Time on scene and transport time to Boston Medical Center will be obtained from the Boston EMS patient care report database. Data will be collected and stored in Microsoft Excel (Redmond, WA) and analyzed using SPSS 27 (Armonk, NY).

Data analysis

A two-sided Student's t-test will be used to examine the primary outcome of time to achieving proper sedation between the two medication. Length of hospital stay and length of time of mechanical ventilation will also be analyzed by a Student's t-test.

Quantitative variables such as AMSS, laboratory values, and vital signs will be analyzed using SPSS with appropriate means, standard deviations and ranges calculated. Descriptive statistics will be used to further characterize patients by demographic features. Secondary outcomes of adverse events, rates of intubation, need for redosing, time of arrival, toxicology report and gender will be analyzed with a Chi-square test and 95% confidence intervals for the difference between two proportions. Note that time of arrival will be defined as day-shift arrival (0700-2259 and overnight-shift arrival (2300-0659), as used by Olives et al.[59]

Timeline and resources

The time course for this study is outlined in Table 5. The study will begin with formal submission of this proposal for approval by the IRB at Boston Medical Center. After the proposal is approved, training of study personnel (paramedics, study coordinators, ED providers, ED nurses, ED pharmacist, ED respiratory therapist) on the AMSS, indications, contraindications and side effects of ketamine and haloperidol will occur.[63,67] All participants will have to pass a 9 question quiz containing example patients with different AMSS scores. A 100% will be required to pass.[1] Once training is complete we will begin patient enrollment for 24 months.

Table 5: Time Course for Study

September 2020	• Institutional Review Board (IRB) submission and approval
September 2020-August 2022	• Subject recruitment and data collection
September 2022- March 2023	• Analysis of results • Preparation and submission of manuscripts for peer review and publication

Institutional Review Board

The study design will be submitted for full and complete review by the Institutional Review Board at Boston Medical Center to ensure the safety of all participants involved in the study. Due to the nature of this study and the inherent risks of administering medication to acutely agitated patients full board review is warranted.

CONCLUSION

Discussion

The common major missing component with prior studies on prehospital use of ketamine is the lack of blinding and randomization. While this study is novel in that it is the first double blind randomized controlled trial comparing prehospital use of ketamine to haloperidol, it is not without limitations. Firstly, the subjects recruited from this study will be from the Boston metropolitan area so it may not be generalizable to other parts of the country, especially more rural parts. If this study demonstrates safety and efficacy, it would be best to examine its application in more rural settings with longer transport times and fewer resources before it's practice could be adopted more widely. Additionally, it

will be impossible to fully control for provider bias and comfort, which will likely impact some secondary outcome measures, most notably intubation rates, which has been seen in many previous studies. We will attempt to remove some of this bias by having a dedicated respiratory therapist available who is an expert in respiratory mechanics and airway management and who is familiar with the administration and side effects of both ketamine and haloperidol for each patient enrolled in the study. However, this will further reduce the generalizability of the study as it is unlikely that hospitals would be able to ensure the availability of a dedicated respiratory therapist for every sedated patient.

While this study will be the first double-blind randomized controlled trial comparing the prehospital use of ketamine to haloperidol it will only add one new data point to the extremely controversial topic of prehospital management of agitation. It is worth noting that verbal de-escalation is an area of study that is frequently left out of the medical curriculum and is often learned through trial and error. It would benefit everyone involved in an agitated patient encounter to have more standardized education on non-physical, non-chemical methods of dealing with an acutely agitated patient. Future research and teaching needs to not only focus on the pharmacologic management of agitation but also pull in experts from the fields on psychiatry and behavioral medicine to help educate providers on the best, most standardized methods of verbal de-escalation. It would also benefit providers to learn from their anesthesia colleagues who are the most experienced using ketamine and would likely be able to alleviate the discomfort of caring for a dissociated patient, ultimately leading to fewer intubations.

There are some significant obstacles we anticipate encountering with this study. Ensuring the safety of providers and subjects is paramount and may limit the number of patients that we are able to enroll. Data collection may be impacted secondary to the severity of the patient's condition, which could limit our final analysis. There is a strong possibility that a substantial amount of unblinding will occur as determined by the primary medical provider to ensure participant safety which might require increasing enrollment to result in a sufficiently powered study.

Summary

The treatment of agitation is a difficult area to study for many reasons. This has led to much of the current treatment algorithms to be based on expert opinion or sub-par studies. While ketamine has been a commonly used drug by anesthesiologists and emergency department providers for years it has yet to see widespread applications in the prehospital environment. This is due to a variety of factors including provider discomfort with ketamine administration and management of the dissociated patient to not wanting to go against common practice, despite conflicting research on the efficacy and safety of those interventions. This study hopes to alleviate some provider discomfort, while further illuminating the advantages of ketamine for the rapid sedation of agitation for optimal patient and provider safety.

Clinical and/or public health significance

When non-pharmacologic methods for behavioral de-escalation fail it is of vital importance to be able to rapidly and safely sedate an agitated patient for the combined safely of all involved. This study will provide vital information on the safety and efficacy

of ketamine as a first line agent for rapid sedation of acutely agitated patients in the pre-hospital environment. It will be the first randomized, controlled, double blind study investigating the use of ketamine compared to haloperidol in the prehospital environment for agitation and will impact prehospital protocols for the treatment and management of agitation. It will aid in the future reduction of harm to medical and law enforcement personnel by violent patients.

LIST OF JOURNAL ABBREVIATIONS

Acad Emerg Med	Academic Emergency Medicine
Am J Emerg Med	American Journal of Emergency Medicine
Anaesth Crit Care	Anaesthesia Critical Care and Pain Medicine
Anesth Essays Res	Anesthesia Essays and Researches
Anesth Prog	Anesthesia Progress
Ann Emerg Med	Annals of Emergency Medicine
Australas J Paramed	Australasian Journal of Paramedicine
Biomed Chromatogr	Biomedical Chromatography
Br J Anaesth	British Journal of Anaesthesia
Br Med J	British Medical Journal
Bull Emerg Trauma	Bulletin of Emergency and Trauma
Can Anaesth Soc J	Canadian Journal of Anesthesia
Clin Toxicol	Clinical Toxicology
Eur J Anaesthesiol	European Journal of Anaesthesiology
Forensic Sci Res	Forensic Science Research
Handb Exp Pharmacol	Handbook of Experimental Pharmacology
J Anal Tox	Journal of Analytical Toxicology
J Am Soc Anesthesiol	Journal of the American Society of Anesthesiologists
J Psychiatric Practice	Journal of Psychiatric Practice
J R Soc Med	Journal of the Royal Society of Medicine
J Res Pharm Pract	Journal of Research in Pharmacy Practice

Neurocrit Care	Neurocritical Care
Nurs Res	Nursing Research
Prehosp Emerg Care	Prehospital Emergency Care
Prim Psychiatry	Primary Psychiatry
West J Emerg Med	Western Journal of Emergency Medicine

REFERENCES

1. 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. doi:10.1016/j.jemermed.2018.07.017

2. Scheppke KA, Braghiroli J, Shalaby M, Chait R. Prehospital Use of IM Ketamine for Sedation of Violent and Agitated Patients. *West J Emerg Med*. 2014;15(7):736-741. doi:10.5811/westjem.2014.9.23229

3. Mion G. History of anaesthesia: The ketamine story – past, present and future. *Eur J Anaesthesiol EJA*. 2017;34(9):571. doi:10.1097/EJA.0000000000000638

4. Domino EF. Taming the Ketamine Tiger. *Anesthesiol J Am Soc Anesthesiol*. 2010;113(3):678-684. doi:10.1097/ALN.0b013e3181ed09a2

5. Ketamine Hydrochloride Injection, USP for Animal Use. Drugs.com. Accessed September 30, 2019. https://www.drugs.com/vet/ketamine-hydrochloride-injection-usp.html

6. Sleigh J, Harvey M, Voss L, Denny B. Ketamine – More mechanisms of action than just NMDA blockade. *Trends Anaesth Crit Care*. 2014;4(2):76-81. doi:10.1016/j.tacc.2014.03.002

7. Mion G, Villevieille T. Ketamine Pharmacology: An Update (Pharmacodynamics and Molecular Aspects, Recent Findings). *CNS Neurosci Ther*. 2013;19(6):370-380. doi:10.1111/cns.12099

8. Sinner B, Graf BM. Ketamine. *Handb Exp Pharmacol*. 2008;(182):313-333. doi:10.1007/978-3-540-74806-9_15

9. Gales DA, Maxwell DS. Ketamine: Recent Evidence and Current Uses. Published online 2018:7.

10. Dinis-Oliveira RJ. Metabolism and metabolomics of ketamine: a toxicological approach. *Forensic Sci Res*. 2017;2(1):2-10. doi:10.1080/20961790.2017.1285219

11. Adamowicz P, Kala M. Urinary excretion rates of ketamine and norketamine following therapeutic ketamine administration: method and detection window considerations. *J Anal Toxicol*. 2005;29(5):376-382. doi:10.1093/jat/29.5.376

12. Milroy C. Karch's Pathology of Drug Abuse. *J R Soc Med*. 2002;95(5):262-263.

13. Grant IS, Nimmo WS, McNicol LR, Clements JA. Ketamine disposition in children and adults. *Br J Anaesth*. 1983;55(11):1107-1111. doi:10.1093/bja/55.11.1107

14. Göktaş EF, Arıöz F. A review of chromatographic methods for ketamine and its metabolites norketamine and dehydronorketamine. *Biomed Chromatogr*. 2018;32(1). doi:10.1002/bmc.4014

15. Bergman SA. Ketamine: review of its pharmacology and its use in pediatric anesthesia. *Anesth Prog*. 1999;46(1):10-20.

16. Systemic Effects of Ketamine. Accessed September 30, 2019. https://www.openanesthesia.org/systemic_effects_of_ketamine/

17. Kurdi MS, Theerth KA, Deva RS. Ketamine: Current applications in anesthesia, pain, and critical care. *Anesth Essays Res*. 2014;8(3):283-290. doi:10.4103/0259-1162.143110

18. Zeiler FA, Teitelbaum J, West M, Gillman LM. The ketamine effect on ICP in traumatic brain injury. *Neurocrit Care*. 2014;21(1):163-173. doi:10.1007/s12028-013-9950-y

19. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. *Am J Emerg Med*. 2008;26(9):985-1028. doi:10.1016/j.ajem.2007.12.005

20. Maneglia R, Cousin MT. A comparison between propofol and ketamine for anaesthesia in the elderly. Haemodynamic effects during induction and maintenance. *Anaesthesia*. 1988;43 Suppl:109-111. doi:10.1111/j.1365-2044.1988.tb09090.x

21. Haas DA, Harper DG. Ketamine: a review of its pharmacologic properties and use in ambulatory anesthesia. *Anesth Prog*. 1992;39(3):61-68.

22. Taylor PA, Towey RM. Depression of Laryngeal Reflexes during Ketamine Anaesthesia. *Br Med J*. 1971;2(5763):688-689.

23. Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. *Can J Anaesth J Can Anesth*. 1989;36(2):186-197. doi:10.1007/BF03011442

24. Aroke EN, Crawford SL, Dungan JR. Pharmacogenetics of Ketamine-Induced Emergence Phenomena: A Pilot Study. *Nurs Res*. 2017;66(2):105-114. doi:10.1097/NNR.0000000000000197

25. Perumal DK, Adhimoolam M, Selvaraj N, Lazarus SP, Mohammed MAR. Midazolam premedication for Ketamine-induced emergence phenomenon: A

prospective observational study. *J Res Pharm Pract*. 2015;4(2):89-93. doi:10.4103/2279-042X.155758

26. White PF, Way WL, Trevor AJ. Ketamine--its pharmacology and therapeutic uses. *Anesthesiology*. 1982;56(2):119-136. doi:10.1097/00000542-198202000-00007

27. Green SM, Rothrock SG, Lynch EL, et al. Intramuscular ketamine for pediatric sedation in the emergency department: safety profile in 1,022 cases. *Ann Emerg Med*. 1998;31(6):688-697. doi:10.1016/s0196-0644(98)70226-4

28. Green SM, Roback MG, Krauss B, et al. Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: an individual-patient data meta-analysis of 8,282 children. *Ann Emerg Med*. 2009;54(2):158-168.e1-4. doi:10.1016/j.annemergmed.2008.12.011

29. Green SM, Clem KJ, Rothrock SG. Ketamine safety profile in the developing world: survey of practitioners. *Acad Emerg Med Off J Soc Acad Emerg Med*. 1996;3(6):598-604.

30. Ketamine: Drug information - UpToDate. Accessed September 24, 2019. https://www.uptodate.com/contents/ketamine-drug-information?search=ketamine&source=panel_search_result&selectedTitle=1~147&usage_type=panel&display_rank=1

31. Kye YC, Rhee JE, Kim K, et al. Clinical effects of adjunctive atropine during ketamine sedation in pediatric emergency patients. *Am J Emerg Med*. 2012;30(9):1981-1985. doi:10.1016/j.ajem.2012.04.030

32. Effectiveness of Atropine and Glycopyrrolate to Reduce Hyper Salivation With Ketamine Sedation - Full Text View - ClinicalTrials.gov. Accessed September 30, 2019. https://clinicaltrials.gov/ct2/show/NCT01191398

33. Oduntan SA, Gool RY. Clinical trial of ketamine (CI-581): a preliminary report. *Can Anaesth Soc J*. 1970;17(4):411-416. doi:10.1007/bf03004705

34. 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. doi:10.1002/phar.2060

35. Takeuchi A, Ahern TL, Henderson SO. Excited Delirium. *West J Emerg Med*. 2011;12(1):77.

36. Gottlieb M, Long B, Koyfman A. Approach to the Agitated Emergency Department Patient. *J Emerg Med*. 2018;54(4):447-457. doi:10.1016/j.jemermed.2017.12.049

37. Lindenmayer JP. The pathophysiology of agitation. *J Clin Psychiatry*. 2000;61 Suppl 14:5-10.

38. Moritz F, Goullé JP, Girault C, Clarot F, Droy JM, Muller JM. Toxicological analysis in agitated patients. *Intensive Care Med*. 1999;25(8):852-854. doi:10.1007/s001340050964

39. Wilson MP, Pepper D, Currier GW, Holloman GH, Feifel D. The Psychopharmacology of Agitation: Consensus Statement of the American Association for Emergency Psychiatry Project BETA Psychopharmacology Workgroup. *West J Emerg Med*. 2012;13(1):26-34. doi:10.5811/westjem.2011.9.6866

40. Hankin CS, Bronstone A, Koran LM. Agitation in the Inpatient Psychiatric Setting: A Review of Clinical Presentation, Burden, and Treatment. *J Psychiatr Pract*. 2011;17(3):170. doi:10.1097/01.pra.0000398410.21374.7d

41. Deal N, Hong M, Matorin A, Shah AA. Stabilization and Management of the Acutely Agitated or Psychotic Patient. *Emerg Med Clin North Am*. 2015;33(4):739-752. doi:10.1016/j.emc.2015.07.003

42. Maguire BJ, O'Meara P, O'Neill BJ, Brightwell R. Violence against emergency medical services personnel: A systematic review of the literature. *Am J Ind Med*. 2018;61(2):167-180. doi:10.1002/ajim.22797

43. Maguire BJ, Smith S. Injuries and Fatalities among Emergency Medical Technicians and Paramedics in the United States. *Prehospital Disaster Med*. 2013;28(4):376-382. doi:10.1017/S1049023X13003555

44. Brice JH, Pirrallo RG, Racht E, Zachariah BS, Krohmer J. M Anagement of the V Iolent P Atient. *Prehosp Emerg Care*. 2003;7(1):48-55. doi:10.1080/10903120390937085

45. Ng AT, Zeller S, Rhoades RW. Clinical challenges in the pharmacologic management of agitation. *Prim Psychiatry*. 2010;17:46-52.

46. Assessment and emergency management of the acutely agitated or violent adult - UpToDate. Accessed October 8, 2019. https://www.uptodate.com/contents/assessment-and-emergency-management-of-the-acutely-agitated-or-violent-adult

47. Nobay F, Simon BC, Levitt MA, Dresden GM. A prospective, double-blind, randomized trial of midazolam versus haloperidol versus lorazepam in the chemical restraint of violent and severely agitated patients. *Acad Emerg Med Off J Soc Acad Emerg Med*. 2004;11(7):744-749. doi:10.1197/j.aem.2003.06.015

48. Korczak V, Kirby A, Gunja N. Chemical agents for the sedation of agitated patients in the ED: a systematic review. *Am J Emerg Med*. 2016;34(12):2426-2431. doi:10.1016/j.ajem.2016.09.025

49. Mason J, Colwell CB, Grock A. Agitation Crisis Control. *Ann Emerg Med*. 2018;72(4):371-373. doi:10.1016/j.annemergmed.2018.08.004

50. Battaglia J. Pharmacological Management of Acute Agitation. *Drugs*. 2005;65(9):1207-1222. doi:10.2165/00003495-200565090-00003

51. Glassman AH, Bigger JT. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. *Am J Psychiatry*. 2001;158(11):1774-1782. doi:10.1176/appi.ajp.158.11.1774

52. Burnett AM, Salzman JG, Griffith KR, Kroeger B, Frascone RJ. The Emergency Department Experience with Prehospital Ketamine: A Case Series of 13 Patients. *Prehosp Emerg Care*. 2012;16(4):553-559. doi:10.3109/10903127.2012.695434

53. Ho JD, Smith SW, Nystrom PC, et al. Successful Management of Excited Delirium Syndrome with Prehospital Ketamine: Two Case Examples. *Prehosp Emerg Care*. 2013;17(2):274-279. doi:10.3109/10903127.2012.729129

54. 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. doi:10.1016/j.ajem.2014.10.016

55. Burnett A, Panchal D, Peterson B, et al. The Administration of Prehospital Ketamine for Chemical Restraint does not Prolong On-Scene Times Compared to Haloperidol Based Sedation. *Australas J Paramed*. 2015;12(1). doi:10.33151/ajp.12.1.8

56. Keseg D, Cortez E, Rund D, Caterino J. The Use of Prehospital Ketamine for Control of Agitation in a Metropolitan Firefighter-based EMS System. *Prehospital Emerg Care Off J Natl Assoc EMS Physicians Natl Assoc State EMS Dir*. 2015;19(1):110-115. doi:10.3109/10903127.2014.942478

57. Calver LA, Stokes B, Isbister GK. Sedation assessment tool to score acute behavioural disturbance in the emergency department. *Emerg Med Australas*. 2011;23(6):732-740. doi:10.1111/j.1742-6723.2011.01484.x

58. Cole JB, Moore JC, Nystrom PC, et al. A prospective study of ketamine versus haloperidol for severe prehospital agitation. *Clin Toxicol*. 2016;54(7):556-562. doi:10.1080/15563650.2016.1177652

59. Olives TD, Nystrom PC, Cole JB, Dodd KW, Ho JD. Intubation of Profoundly Agitated Patients Treated with Prehospital Ketamine. *Prehospital Disaster Med*. 2016;31(6):593-602. doi:10.1017/S1049023X16000819

60. Cole JB, Klein LR, Nystrom PC, et al. A prospective study of ketamine as primary therapy for prehospital profound agitation. *Am J Emerg Med*. 2018;36(5):789-796. doi:10.1016/j.ajem.2017.10.022

61. 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. doi:10.1080/10903127.2018.1501445

62. 2017vitalstats.pdf. Accessed April 21, 2020. https://www.boston.gov/sites/default/files/file/document_files/2018/05/2017vitalstats.pdf

63. Barbic D, Andolfatto G, Grunau B, et al. Rapid agitation control with ketamine in the emergency department (RACKED): a randomized controlled trial protocol. *Trials*. 2018;19(1):651. doi:10.1186/s13063-018-2992-x

64. Heydari F, Gholamian A, Zamani M, Majidinejad S. Effect of Intramuscular Ketamine versus Haloperidol on Short-Term Control of Severe Agitated Patients in Emergency Department; A Randomized Clinical Trial. *Bull Emerg Trauma*. 2018;6(4):292-299. doi:10.29252/beat-060404

65. Andolfatto G, Abu-Laban RB, Zed PJ, et al. Ketamine-Propofol Combination (Ketofol) Versus Propofol Alone for Emergency Department Procedural Sedation and Analgesia: A Randomized Double-Blind Trial. *Ann Emerg Med*. 2012;59(6):504-512.e2. doi:10.1016/j.annemergmed.2012.01.017

66. Cole JB, Moore JC, Nystrom PC, et al. A prospective study of ketamine versus haloperidol for severe prehospital agitation. *Clin Toxicol*. 2016;54(7):556-562. doi:10.1080/15563650.2016.1177652

67. Martel M, Sterzinger A, Miner J, Clinton J, Biros M. Management of acute undifferentiated agitation in the emergency department: a randomized double-blind trial of droperidol, ziprasidone, and midazolam. *Acad Emerg Med Off J Soc Acad Emerg Med*. 2005;12(12):1167-1172. doi:10.1197/j.aem.2005.07.017

CURRICULUM VITAE