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Efficacy of ketamine for initial control of acute agitation in the emergency department: A randomized study

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ABSTRACT

Background: Clinicians often encounter agitated patients, and current treatment options include benzodiazepines and antipsychotics. Ketamine rapidly induces dissociation, maintains cardiovascular stability, spontaneous respirations, and airway reflexes. There are no prospective, randomized studies comparing ketamine to other agents in the initial management of acute agitation in the Emergency Department (ED).
Objective: Determine the efficacy and safety of ketamine compared to parenteral haloperidol plus lorazepam for initial control of acute agitation.
Methods: This study was a prospective, single-institution, randomized, open-label, real world, standard of care pilot study. Adult patients with combative agitation were randomized to ketamine (4 mg/kg IM or 1 mg/kg IV) or haloperidol/lorazepam (haloperidol 5–10 mg IM or IV + lorazepam 1–2 mg IM or IV). The primary outcome was sedation within 5 min, and secondary outcomes included sedation within 15 min, time to sedation, and safety.
Results: Ninety three patients were enrolled from January 15, 2018 to October 10, 2018. Significantly more patients who received ketamine compared to haloperidol/lorazepam were sedated within 5 min (22% vs 0%, $p = 0.001$) and 15 min (66% vs 7%, $p < 0.001$). The median time to sedation in patients who received ketamine compared to haloperidol/lorazepam was 15 vs 36 min respectively ($p < 0.001$). Patients who received ketamine experienced a significant, but transient tachycardia ($p = 0.01$) and hypertension ($p = 0.01$).
Conclusion: In patients with combative agitation, ketamine was significantly more effective than haloperidol/lorazepam for initial control of acute agitation, and was not associated with any significant adverse effects.

1. Introduction

Clinicians in the Emergency Department (ED) often encounter acutely agitated patients that can pose a danger to themselves and other staff. A wide range of factors can play a role in violent behavior including psychiatric illness, chemical intoxication, or acute medical illness [1]. Verbal de-escalation is currently recommended as first-line treatment [1,2]. However, it may be ineffective, and parenteral medication administration may be required to prevent patients from harming themselves or others. Current available options include benzodiazepines such as lorazepam, as well as first-generation antipsychotics such as haloperidol [2,6]. However, benzodiazepines may cause respiratory depression and hypoxia, and antipsychotics may cause QTc interval prolongation, which may precipitate arrhythmias in the case of occult electrolyte abnormalities [6]. Furthermore, the time to maximal effects of intramuscular lorazepam and haloperidol can take up to 20 and 30 min respectively [5,6].

Ketamine is a dissociative agent that is used for procedural sedation as well as an induction agent prior to endotracheal intubation. It acts as an *N*-methyl-D-aspartate (NMDA) receptor antagonist, inducing a dissociative state resulting in analgesia and amnesia. Unlike benzodiazepines, ketamine maintains cardiovascular stability and preserves spontaneous respirations and protective airway reflexes. It also lacks a linear dose-response continuum—once dissociation is achieved at a dose threshold, further doses of ketamine add no additional sedation, and theoretically, has no clinically significant effect on airway integrity and respirations when utilized as monotherapy [1,3]. Ketamine also has a rapid onset of action—within 1 min when administered intravenously, and 5 min when administered intramuscularly [4].

In previous studies, ketamine was evaluated for initial control of agitation in both the pre-hospital and hospital settings, demonstrating quicker time to sedation when compared to other agents. However, some studies noted concerning adverse effects including hypersalivation, vomiting,

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laryngospasm, tachycardia, hypertension, and respiratory depression [1,7-9,16]. These studies provided a basis of evidence supporting its use, but they were all retrospective reviews or prospective observational studies. Even though the pharmacokinetics of ketamine, haloperidol, and lorazepam are well-described, there are no published prospective, randomized studies comparing the safety and efficacy of ketamine to other agents in the initial management of agitated patients in the Emergency Department [3,9-16]. This study was designed to assess the efficacy and safety of parenteral ketamine compared to parenteral haloperidol plus lorazepam for acute agitation.

2. Methods

2.1. Study design

This study was a prospective single-institution, randomized, open-label pilot study that enrolled patients from the Emergency Department of a single tertiary medical center in the United States. This study did not receive any funding, and the design, analysis, and data collection were performed by the primary investigator and co-investigators.

Based on prescribing behavior and evidence from previous studies, the physicians participating in the study agreed that both ketamine and haloperidol plus lorazepam were part of their routine management of acute agitation in the ED. Thus, consent was not obtained as randomization did not affect current prescribing practices for patients to be screened and enrolled. The study design and the waiver of informed consent were both approved by the institutional review board at the facility.

2.2. Selection of participants

Patients were eligible to participate in the study if they were at least 18 years old and admitted to the Emergency Department with an active diagnosis of combative agitation as diagnosed by Emergency Department clinician. The inclusion criteria were selected because patients who are combative present an urgent danger to themselves and to staff, and require rapid intervention to provide them care in a timely fashion and to maintain staff safety. Eligible patients were identified by physicians participating in the study. Patients were excluded from the study if they were younger than 18 years or had a known diagnosis of pregnancy, schizophrenia, angina, uncontrolled hypertension, heart failure, glaucoma/ocular injury, or thyroid disorder [3]. These exclusion criteria were based off the published guidelines on the use of ketamine for dissociative sedation [7-9,16].

This study was a real-world evaluation of standard of care practice for the treatment of acute, combative agitation in patients in the ED. A group of core ED physicians at the study site who agreed that both ketamine and haloperidol plus lorazepam were part of their routine management of acute agitation participated in enrolling and randomizing patients to either arm of the study.

2.3. Randomization and interventions

ED physicians were educated on eligibility, randomization, and study medications, and nurses were educated on eligibility, medication administration, and monitoring/documentation requirements. ED physicians screened patients for eligibility, and participating physicians randomized patients to receive either ketamine or haloperidol plus lorazepam. Physicians and study investigators randomized patients using a computer-generated random-number table. A permuted-block design with blocks of 20 was used to create random-number tables that were posted in each of the five Emergency Department pods. It was elected to post the randomization tables to allow for physicians to anticipate what agent to administer when a combative patient presented, and facilitated expeditious treatment for these patients. Subjects, physicians, and the investigators were not blinded to study drug assignment, and subjects' medical records were reviewed to ensure the medication was received.

Patients randomized to the ketamine arm received 4 mg/kg IM (maximum 500 mg) or 1 mg/kg IV. Patients randomized to the haloperidol plus lorazepam arm received haloperidol 10 mg IM or IV and lorazepam 2 mg IM or IV. Prior to arrival, paramedics have standing orders for midazolam 5 mg IM once as needed for agitation, which could be repeated for an additional dose in 10 min. If patients received midazolam in the field prior to randomization, were hypoxic or at risk for respiratory depression, or were overtly intoxicated, physicians had the option to either omit or lower the dose of lorazepam to 1 mg. Physicians also had the option to lower the dose of haloperidol to 5 mg for patients weighing <60 kg, age ≥ 80 years, or in the presence of significant medical comorbidities (Fig. 1).

2.4. Measurements

Once study medications were administered, nurses assessed the sedation level of each patient using the Richmond Agitation and Sedation Scale (RASS) score, vital signs, as well as any adverse effects according to standard of practice. After the patient was adequately sedated or if adequate sedation was not achieved within 5 min of study drug administration, selection of additional medications to control agitation was left to physician discretion.

Demographic data, such as patient age at admission, sex, and race were collected on each eligible patient through review of the medical record. To address patient safety, we also collected patient vitals data which included: heart rate, blood pressure, respiratory rate, corrected QT interval (QTc), and oxygen saturation. Comorbidity data (diabetes, coronary artery disease [CAD], hypertension, hyperlipidemia, congestive heart failure [CHF], human immunodeficiency virus [HIV], lung disease, psychiatric diagnosis), and substance use prior to admission (methamphetamines/amphetamines, alcohol, cannabinoids) were identified from the patient history or via serum and/or urine laboratory results.

2.5. Outcomes

The primary outcome measure chosen for the study was adequate sedation within 5 min, defined by a documented RASS score of less than or equal to 0 or nursing narrative documentation. The RASS score was selected as a primary outcome measure based on its widespread multidisciplinary use, ease of assessment, and routine use as the standard of care for sedation assessment in the Emergency Department [16]. A score of 0 indicates the patient is alert and calm; scores < 0, ranging from −1 to −5 indicate increasing levels of sedation and decreased responsiveness to voice or touch. Nurses from each shift were trained in 3 training sessions on the study protocol and documentation. They were instructed to chart the RASS at the first point of adequate sedation, as charting and documentation takes a lower priority while sedation is being administered to the agitated patient.

Secondary outcomes included adequate sedation within 15 min, time to sedation, median RASS score at 30 min, and whether additional sedation medications were administered within 30 min. Adverse events documented included tachycardia, hypertension, hypoxia, QTc > 450 ms, arrhythmia, cardiac arrest, respiratory depression requiring endotracheal intubation, and patient-reported nausea. If adverse effects could not be assessed due to lack of data (i.e. no electrocardiogram to assess QTc, no vital signs charted within 2 h), these patients were not included in the analysis of the incidence of that adverse effect.

2.6. Statistical analysis

Statistical design was based on previous studies assessing ketamine for acute agitation that demonstrated median times to sedation of 5–15 min. We estimated a difference of 30% in the primary outcome

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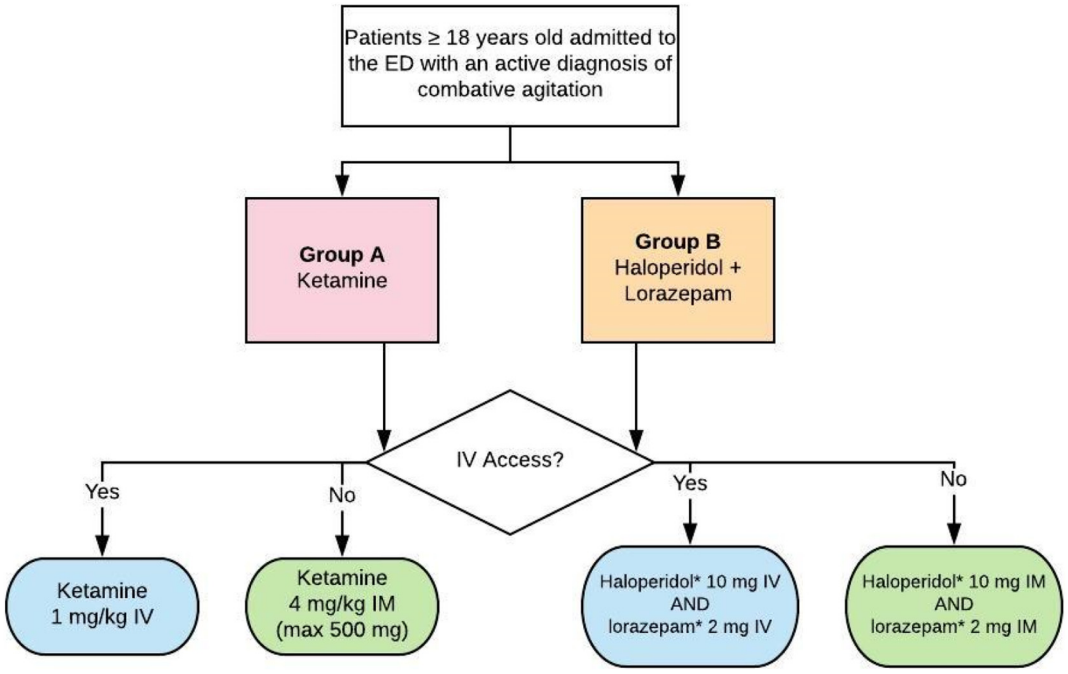

Fig. 1. Patient recruitment and randomization diagram. *Haloperidol dose may be lowered to 5 mg at the physicians' discretion for patients <60 kg, >80 y/o, or significant medical comorbidities. *Lorazepam dose may be lowered to 1 mg, or omitted at the physician's discretion if the patient had received midazolam prior to admission, is overtly intoxicated, or at risk for hypoxia/respiratory depression.

(adequate sedation within 5 min) between ketamine versus haloperidol and lorazepam [10,11,15]. Based off that, a sample size of 84 patients would be necessary to detect a 30% difference with a one-sided $\alpha = 0.05$ and statistical power of 80%. In anticipation that some patients would be excluded due to protocol violations or other factors, the initial enrollment goal was 100 subjects. Enrollment was stopped on October 10, 2018, prior to reaching target enrollment due to a low number of protocol violations.

Results are displayed as means (standard deviation [SD]), medians (interquartile ranges [IQR]), or percentages, as appropriate. We first evaluated the bivariate association between each variable and treatment group using *t*-tests, rank sum tests, and Fisher's exact tests. To address our primary objective and assess for the presence of confounders, we subsequently evaluated the bivariate association between treatment group, demographic variables, and safety variables and the primary and secondary outcomes using the same statistical methods as previously noted. Mean and median time to sedation by treatment group were assessed using the *t*-test and rank sum tests, respectively. Statistical significance was attributable to a p-value of <0.050. Data were analyzed using Stata MP version 13.1 (StataCorp LLC, College Station, TX).

3. Results

3.1. Study patients and baseline demographics

From January 15, 2018 through October 10, 2018, 93 patients were enrolled at the study site. Only a core group of ED physicians who agreed that the agents in both study arms were part of their routine management of acute agitation participated in enrolling and randomizing patients, so the total number of patients screened in the study is unknown. However, for perspective, in that time frame, a total of 152 patients received sedative medications for agitation/aggressive behavior. A total of 44 patients were randomized to receive ketamine and 49 patients were randomized to receive haloperidol plus lorazepam.

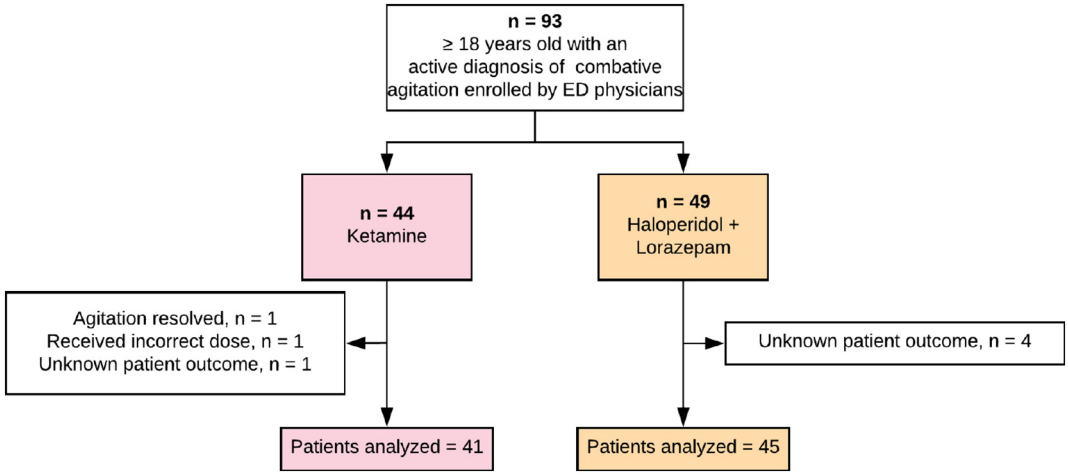

Fig. 2. Patient enrollment and analysis.

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Table 1
Baseline demographics.

		Total (n = 93)	Ketamine (n = 44)	Hal + Lor (n = 49)
Median age (years)		39 (19–92)	37 (19–67)	45 (19–92)
Male – % (no.)		62% (58)	68% (30)	57% (28)
Race - % (no.)	White	58% (54)	66% (29)	51% (25)
	Black	14% (13)	9% (4)	18% (9)
	Hispanic	18% (17)	16% (7)	20% (10)
Median HR (bpm)		101	110	100
Median BP (mm Hg)		130/78	132/88	134/79
Comorbidities % (no.)	Diabetes	10% (9)	9% (4)	10% (5)
	CAD	3% (3)	2% (1)	4% (2)
	Hypertension	11% (10)	11% (5)	10% (5)
	Hyperlipidemia	3% (3)	2% (1)	4% (2)
	CHF	3% (3)	0% (0)	6% (3)
	HIV	2% (2)	2% (1)	2% (1)
	Lung disease	3% (3)	5% (2)	2% (1)
	Psychiatric condition	56% (52)	43% (19)	67% (33)

Of the 44 patients randomized to ketamine, 3 were excluded, and of the 49 patients randomized to haloperidol plus lorazepam, 4 were excluded (Fig. 2). The median age of the patients was 39 years (range 19–92), and baseline demographics, comorbidities, and vital signs were well matched between both groups (Table 1). Despite excluding patients with known schizophrenia, 56% of patients enrolled were later found to have a history of psychiatric disease, such as depression, anxiety, bipolar disorder, or schizophrenia.

The majority of patients (93%) enrolled in the study were administered medications intramuscularly, most commonly for a diagnosis of acute agitated delirium or acute agitation (Fig. 3). Of the patients who were randomized to the haloperidol plus lorazepam arm, 61% of patients received the goal dose of haloperidol 10 mg and lorazepam 2 mg, and 20% of patients received a dose of haloperidol 5 mg and lorazepam 2 mg—doses were adjusted based off patient comorbidities, weight, and medications/ingestants prior to admission (Fig. 1, Table 2). The most common ingestants from patient history and laboratory results across both groups was methamphetamines/amphetamines, alcohol, or cannabinoids.

3.2. Clinical outcomes

In this study, 22% of patients in the ketamine group achieved the primary outcome of sedation within 5 min, compared to 0% of patients in the haloperidol plus lorazepam group ($p = 0.001$). Furthermore, 66% of patients in the ketamine group were sedated within 15 min, compared to 7% of patients in the haloperidol plus lorazepam group ($p < 0.001$). The median time to sedation was 15 min for patients in the ketamine group, and 36.5 min for patients in the haloperidol plus lorazepam group ($p < 0.001$). The median RASS score achieved at 30 min in the ketamine group was −1, and in the haloperidol plus lorazepam group was 0 ($p = 0.016$). Thus, ketamine resulted in both more rapid and deeper sedation compared to haloperidol plus lorazepam (Table 3). These outcomes did not vary significantly in relation to presenting diagnosis or ingestants prior to admission.

3.3. Safety

Hypertension, defined as an increase in blood pressure (systolic or diastolic) > 20 mm Hg, and tachycardia, defined as an increase in HR > 10 bpm, were significantly more common in patients who were randomized to ketamine ($p = 0.014$, 0.012). For the majority of patients, the hypertension/tachycardia resolved prior to leaving the Emergency Department. There was no significant difference between other adverse effects such as QTc > 450 ms, hypoxia, hypotension, nausea, and hypersalivation (Table 4).

The incidence of hypoxia ($SpO_2 < 92\%$) was higher in the ketamine group compared to the haloperidol plus lorazepam group (21% vs 10%), but this was not statistically significant ($p = 0.238$). In most cases, the hypoxia resolved with minor and noninvasive interventions

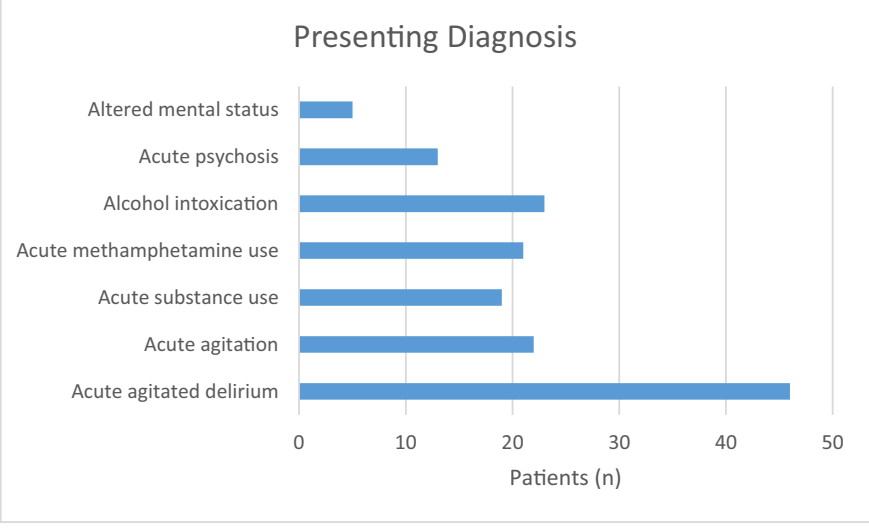

Fig. 3. Presenting diagnosis of patients enrolled in the study.

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Table 2
Medication administration and dosage distribution.

	Total (n = 93)	Ketamine (n = 44)	Hal + Lor (n = 49)
IV	6.5% (6)	5% (2)	8% (4)
IM	93.5% (86)	95% (42)	92% (45)
Ketamine dose			
1 mg/kg IV		5% (2)	
4 mg/kg IM		95% (40)	
Haloperidol/lorazepam doses[a]			
5 mg/1 mg			10% (5)
5 mg/2 mg			20% (10)
10 mg/2 mg			61% (30)

[a] Only dosages > 1 patient in that patient group displayed.

such as supplementary oxygen via nasal cannula, but did result in intubation in one patient in the ketamine group. In the ketamine group, if patients experienced hypoxia, there was a nonsignificant higher likelihood that the patient had a detectable blood alcohol level ($p = 0.058$).

One episode of 4–5 beats of non-sustained ventricular tachycardia also occurred in the ketamine group—the patient was admitted to the inpatient ward, and continued to have non-sustained ventricular tachycardia until his/her electrolyte abnormalities were corrected. One patient with an unknown identity and medical history at time of presentation was randomized to haloperidol plus lorazepam and experienced bradycardia, hypoxia, cardiac arrest, and subsequent death after medication administration. After investigation, it was found that this patient had a longstanding history of methamphetamine abuse and pulmonary hypertension, and in discussion with the investigators, participating physicians, and the institutional review board, it was deemed that the adverse event was possibly related to the haloperidol plus lorazepam. However, given the clinical situation and unknown identity/medical history, it was concluded that the patient's management would not have changed.

Emergence reactions are defined as a sensation of unpleasant dreams, delirium, and hallucinations after returning to baseline from dissociation. Though emergence reactions are well-documented when ketamine is used for anesthesia/sedation, when used for agitation, it is difficult to ascertain whether patients had returned to their agitated baseline or were experiencing a new emergence reaction. Similar to the majority of previous studies of ketamine for agitation, no emergence reactions were documented during the study [1,7-9].

4. Discussion

In this randomized, prospective study of ketamine for the initial control of acute agitation in the Emergency Department, ketamine was significantly more effective than haloperidol plus lorazepam at adequately sedating patients within 5 min and 15 min. Patients were most commonly admitted to the Emergency Department for acute agitation, oftentimes due to ingestion of amphetamines, alcohol, or cannabinoids.

Table 3
Efficacy outcomes.

	Ketamine (n = 41)	Hal + Lor (n = 45)	p-Value
Primary endpoint			
Sedation within 5 min	22%	0%	$p = 0.001$
Secondary endpoints			
Sedation within 15 min	66%	7%	$p < 0.001$
Median time to sedation	15 min	36.5 min	$p < 0.001$
Median RASS at 30 min	−1	0	$p = 0.020$
Additional sedative medications required within 30 min	22%	20%	$p = 0.824$

Many patients enrolled into the study had a history of a psychiatric disorder at baseline, including schizophrenia and schizoaffective disorder. In many instances, this history was not available during the patient's initial presentation, but was discovered later in the medical record or upon interview once the patient was cooperative. Administration of ketamine in this study was not associated with any documented emergence reactions or increase in psychosis.

The administration of ketamine was also associated with significantly shorter time to sedation compared to haloperidol plus lorazepam, and was associated with a deeper sedation as well. Despite dosing variability in the haloperidol/lorazepam group due to patient comorbidities, history and variable ingestants, the majority of patients (81%) did receive haloperidol 5–10 mg and lorazepam 2 mg. Ketamine was associated with a significantly increased incidence of tachycardia and hypertension, and a nonsignificant increase in the incidence of hypoxia. When ketamine is utilized as a monotherapy for sedation, its effects are more predictable and it has been shown to preserve respiratory drive. However, when other respiratory depressants such as alcohol are also present, it is possible that it produces a synergistic effect that decreases respiratory drive and causes hypoxia. Larger studies will be required to elucidate this mechanism and its clinical relevance.

This study was the first randomized, prospective study on the efficacy and safety of ketamine for agitation in an Emergency Department setting. However, this study did have some limitations. The study did not screen all patients who came to the Emergency Department with acute agitation—rather, it was a core group of physicians who agreed that agents in both arms were part of their routine management of acute agitation who enrolled. During the study timeframe, 152 patients received medications for agitation/aggressive behavior. Unfortunately, one of the study limitations is that reasons for excluding these patients are unknown—a contributing factor could be physicians' experience or comfort level with the study medications, so this could have resulted in some selection bias. Furthermore, at the institution where the study was performed, documentation of medication administration, sedation, vital signs, and adverse effects was dependent on nursing education, evaluation, and charting. Thus, there could be variability in time to nursing assessment and documentation of sedation. Data collection and analysis was not blinded, and could have introduced potential bias into the study analysis. Lastly, this study did not assess whether more rapid time to sedation was associated with a shorter length of ED stay.

In summary, in this randomized, prospective, open-label study of ketamine compared to haloperidol plus lorazepam for the initial control of acute agitation, ketamine was associated with a significantly greater proportion of patients adequately sedated at 5 min and 15 min, as well as a shorter time to sedation.

CRediT authorship contribution statement

Justin Lin: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft, Visualization. **Yelena Figuerado:** Conceptualization, Methodology, Resources, Writing - review & editing.

Table 4
Safety outcomes.

	Ketamine (n = 44)		Hal + Lor (n = 49)		p-Value
	%	n	%	n	
Hypertension (Δ > 20 mm Hg)	33	13/39	11	4/35	$p = 0.012$
Tachycardia (Δ > 10 bpm)	34	13/38	11	4/35	$p = 0.014$
Hypoxia ($SpO_2 < 92\%$)	21	6/39	10	3/42	$p = 0.238$
QTc > 450 ms	48	11/23	50	11/22	$p = 0.884$
Nausea/vomiting	2	1/44	0	0/49	$p = 0.937$
Intubation	2	1/44	2	1/49	$p = 0.940$
Arrhythmia	2	1/44	2	1/49	$p = 0.940$
Cardiac arrest	0	0/44	2	1/49	$p = 0.946$

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Adrienne Montgomery: Conceptualization, Methodology, Resources, Writing - review & editing. **Jonathan Lee:** Conceptualization, Methodology. **Mark Cannis:** Methodology, Writing - review & editing. **Valerie C. Norton:** Methodology, Writing - review & editing. **Richard Calvo:** Methodology, Formal analysis, Writing - review & editing. **Harminder Sikand:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration.

Declaration of competing interest

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Appendix A

Richmond Agitation and Sedation Scale (RASS)		
+4	Combative	Overtly combative or violent, immediate danger
+3	Very agitated	Pulls on or removes tubes or catheters, aggressive
+2	Agitated	Frequent non-purposeful movement
+1	Restless	Anxious or apprehensive but movements not aggressive
0	Alert and calm	
−1	Drowsy	Not fully alert, sustained (>10 s) awakening, eye contact to voice
−2	Light sedation	Briefly (<10 s) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

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