Submitted: 17 December, 2023 Accepted: 06 February, 2024 Online Published: 31 May, 2024 DOI:10.22514/sv.2024.066

Open Access
Signa Vitae

ORIGINAL RESEARCH

The effective dose of ketamine in the management of acute agitation in emergency departments

Sultan Alghadeer[1,*], Ghadeer A. Alhamid[1], Rana Almotawa[1], Abeer Alshareef[2], Mohmad A. Knas[3], Saqer Althunayyan[4]

[1]Department of Clinical Pharmacy, College of Pharmacy, King Saud University, 12372 Riyadh, Saudi Arabia
[2]Corporate of Pharmacy Services, King Saud University Medical City, 12372 Riyadh, Saudi Arabia
[3]Al-Habib Medical Group, 12214 Riyadh, Saudi Arabia
[4]Department of Trauma, Prince Sultan College for EMS, King Saud University, 12642 Riyadh, Saudi Arabia

***Correspondence**
alghadeer@ksu.edu.sa
(Sultan Alghadeer)

Abstract

Ketamine therapy is considered a novel treatment for agitation. Ketamine has a rapid onset and short half-life, can be administered in various formulations, and delivers sedation reliably with a single dose. However, providing a well-defined dose of ketamine for acute agitation, particularly as an intravenous (IV) bolus, is questionable. This study aims to define an effective dose of ketamine for treating acute agitation in the emergency department (ED). A multi-center retrospective observational study was conducted from June 2015 to March 2022 to examine agitated patients presented to four EDs in Saudi Arabia and were administered ketamine as the initial calming medication. The study included a total of 20 patients, most of whom were males (70%) in their adult ages (65%) who were mainly presented to the ED with behavioral, cognitive or psychiatric disorders (55%). Only six patients (28.6%) needed an additional calming agent. The 50 mg IV bolus was the most common initial (n = 6) and cumulative (n = 5) fixed dose and achieved a success rate of 66.7% in both doses. The most common initial weight-based dose was 0.5 mg/kg in 7 cases (71.4% success rate), followed by 0.7–0.8 mg/kg in 6 cases (66.7% success rate). Meanwhile, the doses 0.5 mg/kg in 6 cases (83.3% success rate) and 0.7–0.8 mg/kg in 6 cases (66.7% success rate) were major cumulative weight-based doses. The results were interpreted using descriptive statistics. Overall, ketamine showed neutral effects on the respiratory and cardiac markers. It is seldom used as an initial medication for acute agitation in the ED. A starting dose of 0.5–1 mg/kg or 50 mg of ketamine as an IV bolus injection showed reasonable effectiveness and appropriate safe properties in calming agitated patients in the ED.

Keywords

Ketamine; Agitation; Emergency; Dose; Medication

1. Introduction

Emergency departments (ED) frequently encounter agitated and aggressive patients worldwide [1–3]. Their violent behavior and extreme agitation are attributed to a variety of causes, and only a small proportion of patients with agitation presents extremely violent behavior, including uncontrollable psychomotor agitation and delirium. This condition is commonly referred to as excited delirium syndrome [1, 4–6]. Agitated patients in EDs must be rapidly assessed to determine the provoked causes and may need an initial calming using verbal or behavioral approaches before performing pharmacological interventions with calming agents such as benzodiazepines (BDZs), antipsychotics (APs), or ketamine [7]. Ketamine therapy is considered a novel treatment for analgesia and severe agitation/excited delirium syndrome. Ketamine is an N-methyl-D-aspartate receptor antagonist that exhibits dissociative sedation and analgesic effects [8–10].

Ketamine has a rapid onset and short half-life, delivers sedation reliably with a single dose, and can be administered in various formulations based on the patient's condition [11]. The sympathetic effect of ketamine may lead to a brief elevation in cardiac markers secondary to increasing myocardial oxygen consumption and may cause ischemic events [12, 13]. However, it generally maintains cardiovascular stability and preserves spontaneous respirations and protective airway reflexes, justifying its use in treating severe asthma, especially in the pediatric population. Theoretically, it has no clinically significant effect on airway integrity and respirations when utilized in monotherapy [14]. It showed a positive respiratory impact by inducing bronchodilation and decreasing the risk of respiratory depression [15], but it may not be suitable for patients in a dissociative state who are unable to participate in their own care [16]. Ketamine has a non-linear dose–response relationship, so once dissociation is achieved at a dose threshold, further doses of ketamine add no additional sedation [17].

The therapeutic range of ketamine in managing acute agi-

tation varies from one study to another, and the optimal dose varies as well [18]. At high doses (1–2 mg/kg intravenous (IV) dose or 3–5 mg/kg intramuscular (IM) dose), ketamine can induce dissociation and amnesia, making it ideal for moderate sedation in the emergency department. However, high doses were associated with a high risk of endotracheal intubation, which led to using 2 mg/kg IM dosing to minimize the risk and achieve adequate sedation [18]. At low doses (or sub-dissociative dosing), it produces analgesia with reports of different onsets and durations of actions [18–20].

Ketamine usage for acute agitation in EDs may seem low [21]. This could be because ketamine does not treat the underlying cause of agitation if its etiology persists; this may necessitate multiple doses of additional calming medications [8]. On the other hand, the fast onset and short duration of action along with its acceptable safety properties make ketamine an optimal choice for managing acute agitation in EDs [11]. Therefore, several studies have assessed the efficacy and safety of ketamine for acute agitation management in EDs and proposed a dose range of 1–2 mg/kg as an IV bolus injection and 4–6 mg/kg as an IM injection [14, 17, 21–23], although the patients included in most of these studies were administered ketamine as IM. A recent randomized clinical trial found that a ketamine dose of 5 mg/kg IM is a safe and effective short-acting sedating agent [24]. Additionally, the American College of Emergency Physicians (ACEP) guidelines for agitation management recommend a ketamine dose of 5 mg/kg as IM and 1–2 mg/kg as an IV bolus agent [25]. Some recommendations advised not exceeding 4 mg/kg IM, and one suggested restricting the dose to 2 mg/kg IM to limit the need for subsequent endotracheal intubation [26]. Notably, very few studies examined patients who took ketamine as an IV bolus for acute agitation. In such studies, a wide range of 0.3–2.2 mg/kg was reported [14, 17]. A recent randomized clinical trial proposed 0.5 mg/kg as an effective IV bolus dose of ketamine, but in combination with haloperidol [27]. However, despite the clinical usage of ketamine for agitation control in EDs, using well-defined doses of ketamine for acute agitation, particularly as an IV bolus, is questionable. Therefore, this study aims to define an effective dose of ketamine for treating acute agitation in the ED.

2. Materials and methods

A multi-center retrospective observational study was conducted from June 2015 to March 2022 to examine agitated patients who were presented to EDs and administered ketamine for sedation. The involved hospitals were the King Saud University Medical Center (KSUMC) including its both hospitals (King Khalid University Hospital and King Abdulaziz University Hospital) and the Al-Habib Medical Group (HMG) including its four branches in Riyadh (Rayan, Olaya, Al-Sweidi and Al-Takhassusi). All these hospitals are located in Riyadh, Saudi Arabia.

Any patient who had presented to the ED with acute agitation, defined by the Richmond Agitation-Sedation Scale (RASS) as $\geq$+2, for which ketamine was administered as the initial calming medication was included in the study. However, pregnant or breastfeeding women and patients with hypersensitivity or allergy to ketamine, schizophrenia, acute pulmonary insufficiency, severe chronic obstructive pulmonary disease, acute narrow-angle glaucoma or a history of a cerebrovascular accident were excluded. Additionally, the exclusion criteria included incomplete patient care record or irretrievable chart and ketamine being given for any other reason than agitation/excited delirium syndrome.

The study's primary objective was to investigate the effective ketamine dose for agitated patients in the emergency department. The effective dose of ketamine was determined by achieving successful sedation as documented by an emergency physician. Additionally, the study aimed to assess ketamine's effect/safety on the cardiopulmonary system by examining vital signs data including heart rate (HR), blood pressure (BP), respiratory rate (RR), and oxygen saturation (OS) before and 4 hours after administering. Data was taken four hours after ketamine administration in similar studies, as ketamine may asymptomatically raise the vitals immediately after administration and it will take 4 hours to return to normal [8, 28]. These data were obtained from the patient files kept in each hospital. The other collected data include patient demographics (such as age, gender and body mass index (BMI)), the chief complaint for ED presentation, RAAS score, indication for ketamine, initial ketamine dose, minimum, maximum and cumulative ketamine dose administered, frequency of ketamine administration, ketamine administration route and time, total duration of ketamine therapy, emergency department or hospital length of stay, discharge disposition, additional administration of APs or BDZs, and the additional provision of calming medication within 1–3 hours preceding ketamine administration (including route/dose/time). All data were entered into an Excel spreadsheet (version 2023, Microsoft, Redmond, WA, USA), where basic descriptive statistics was performed. Continuous variables were described as means and standard deviation values, whereas categorical variables were expressed as counts and percentages.

3. Results

A total of 20 patients were confirmed to receive ketamine in the ED for a definite diagnosis of agitation after ensuring hemodynamic stability and ruling out a differential diagnosis. Most of the study subjects were adult males and were mainly presented to the ED with behavioral, cognitive or psychiatric disorders. Refer to Table 1 for more information.

The initial ketamine dose was not an agitation controller in four patients (3 patients through IV bolus and 1 through IM), and subsequent ketamine doses were needed. Moreover, only six patients (30%) needed an additional calming agent within 1–3 hours after the ketamine's effect wore off.

The most common initial fixed dose was 50 mg. Such dose was used in 7 cases; 6 were administered IV and on IM. Of those administered 50 mg IV, two out of six (66.7% success rate) were required to be on either BDZs or APs. The 50 mg IM dose failed to achieve sedation, hence requiring subsequent doses and additional calming medications. The range of the initial fixed dose was 20–70 mg. An initial low fixed dose (20 mg) was administered in two cases (one of which was pediatric). Both failed to manage agitation, and second doses

TABLE 1. Demographic characteristics (n = 20).

Demographic characteristics	Cases	Notes
Age		
Children (1–12)	2	One 7 years old male (with PMH of ADHD) and one 9 years old female (with no previous PMH).
Adolescents (13–17)	2	One 13 years old male (with PMH of HSV encephalitis on antipsychotic) and one 13 years old female (first time seizure with no previous PMH).
Early adulthood (18–39)	8	
Middle adulthood (40–59)	5	
Elderly (≥60)	3	Three young elderly (60–74 years) and one ≥75 years.
Gender		
Male	14	
Female	6	
BMI		
Under-weight (<18.5 kg/m^2)	2	Both females.
Normal weight (18.5–24.9 kg/m^2)	8	
Overweight (25 to 29.9 kg/m^2)	5	
Obesity (≥30 kg/m^2)	5	Class I (30–34.9) = 2; class II (35–39.9) = 2; class III (> or = 40) = 1
Chief complain for ED admission		
Behavioral, cognitive or psychiatric disorders	11	Included new or serious onset of behavioral/mental changes or aggressiveness; 2 cases of children and one case of adolescent.
Neurological disorders	3	Two patients presented with headache (one with definite diagnosis of migraine and another with cluster headache); one adolescent case of new onset of seizure prior to ED arrival with no previous PMH.
Pain or trauma	3	Two patients with definite diagnosis of SCA; once case post RTA.
Cardiovascular diseases	2	One case with decompensated HF; another case with IHD and valvular abnormality.
Multiple drugs intoxication	1	Overdose of cannabis, pregabalin and alprazolam.

ADHD: attention deficit hyperactivity disorder; BMI: body mass index; ED: emergency department; HF: heart failure; HSV: herpes simplex virus; IHD: ischemic heart disease; PMH: past medical history; RTA: road traffic accident; SCA: sickle cell anemia.

were administered. Further, 50 mg in 6 cases, 25 mg in 5 cases and 40 mg in 3 cases were the major cumulative fixed doses with a dosage range between 25 and 120 mg. Notably, the 50 mg dose induced sedation in 4 out of 6 patients (66.7%) without additional calming drugs.

The most common initial weight-based dose was 0.5 mg/kg in 7 cases (5 (71.4%) of which achieved sedation from the initial dose), followed by 0.7–0.8 mg/kg in 6 cases (4 (66.7%) of which achieved sedation from the initial dose) and 0.3–0.35 mg/kg in 4 cases. The range of initial weight-based dose was 0.3–1.3 mg/kg. The initial low weight-based dose (0.3 mg/kg) failed to manage agitation in 2 of 3 cases (one of which was administered IM). Regarding cumulative weight-based doses, the doses 0.5 mg/kg in 6 cases (83.3% success rate) and 0.7–0.8 mg/kg in 6 cases (66.7% success rate) were the major ones with a dosage range between 0.3 and 2.2 mg/kg. The ketamine dose regimen is listed in Table 2.

Overall, ketamine showed neutral effects on the respiratory and cardiac markers such the RR, OS, HR and BP (Table 3). The average of pre- versus post-administration effect of ketamine on respiratory markers such as RR and OS was 21.4 ± 4.2 versus 19.4 ± 2.2 and 95.01% ± 0.1 versus 98% ± 0.2 respectively, with no cases of hypoxia or hyperventilation. The HR average of pre- versus post-administration of ketamine was 92.9 ± 20.6 versus 84.5 ± 15.8, while the systolic BP average of pre- versus post-administration of ketamine was 124.5 ± 20.1 versus 125 ± 26.4 with mostly no clinically significant sequelae. Despite presenting decompensated HF (case #5), a beneficial elevation in BP and a decline in HR were noted. An increase in BP was also observed in cases #2 and 3 who received a total IV dose of ≥1 mg/kg or >50 mg. No other interventions such as fluid administration, oxygen therapy, vasopressor therapies or other therapies that might impact the vitals were given to the patients within four hours of ketamine administration. No other significant adverse effects were documented.

TABLE 2. Ketamine dose regimen for agitation management (n = 20).

Case (gender, age in years)	Initial ketamine dose (mg/kg)	Additional ketamine dose administered (mg/kg)	Ketamine cumulative dose	Ketamine administration route/Frequency	Emergency department or hospital length of stay	Administration of APs or BDZs within 1–3 hours of ketamine administration
1 (M, 32)	30 mg (0.4 mg/kg)	-	30 mg (0.4 mg/kg)	IV bolus once	1 d	-
2 (M, 24)	70 mg (1 mg/kg)	-	70 mg (1 mg/kg)	IV bolus once	1 d	Midazolam 5 mg IV bolus (3 mg followed by 2 mg)
3 (F, 41)	70 mg (1.3 mg/kg)	50 mg (0.9 mg/kg)	120 mg (2.2 mg/kg)	IV bolus twice (15 min apart)	25 d	Lorazepam 1 mg IV bolus
4 (M, 32)	50 mg (0.7 mg/kg)	-	50 mg (0.7 mg/kg)	IV bolus once	1 d	Midazolam 10 mg IV bolus (2 doses of 5 mg)
5 (M, 45)	39.5 mg (0.5 mg/kg)	-	39.5 mg (0.5 mg/kg)	IV bolus once	30 d; then died	-
6 (M, 34)	50 mg (0.5 mg/kg)	-	50 mg (0.5 mg/kg)	IV bolus once	1 d	-
7 (M, 39)	50 mg (0.3 mg/kg)	50 mg (2 doses)	150 mg (1 mg/kg)	IM 3 doses (one hour apart)	41 d	Haloperidol 5 mg IV 3 doses; diazepam 10 mg IM
8 (M, 71)	50 mg (0.7 mg/kg)	-	50 mg (0.7 mg/kg)	IV bolus once	60 d	Midazolam 3 mg IV bolus
9 (F, 16)	25 mg (0.7 mg/kg)	-	25 mg (0.7 mg/kg)	IV bolus once	1 d	-
10 (F, 21)	50 mg (0.8 mg/kg)	-	50 mg (0.8 mg/kg)	IV bolus once	6 h	-
11 (M, 7)	20 mg (0.5 mg/kg)	15 mg (0.4 mg/kg)	35 mg (0.9 mg/kg)	IV bolus twice (within one hour)	4 d	-
12 (F, 58)	40 mg (0.5 mg/kg)	-	40 mg (0.5 mg/kg)	IV bolus once	2 d	Midazolam 5 mg IV bolus; haloperidol 5 mg IV bolus
13 (M, 13)	25 mg (0.75 mg/kg)	-	25 mg (0.75 mg/kg)	IV bolus once	6 h	-
14 (M, 34)	20 mg (0.3 mg/kg)	20 mg (0.3 mg/kg)	40 mg (0.6 mg/kg)	IV bolus twice (within one hour)	6 h	-
15 (F, 9)	25 mg (0.5 mg/kg)	-	25 mg (0.5 mg/kg)	IV bolus once	7 d	-
16 (F, 70)	50 mg (0.5 mg/kg)	-	50 mg (0.5 mg/kg)	IV bolus once	30 d	-
17 (M, 42)	30 mg (0.5 mg/kg)	-	30 mg (0.5 mg/kg)	IV bolus once	2 d	-
18 (M, 66)	50 mg (0.75 mg/kg)	-	50 mg (0.75 mg/kg)	IV bolus once	2 d	-
19 (M, 34)	25 mg (0.4 mg/kg)	-	25 mg (0.4 mg/kg)	IV bolus once	6 h	-
20 (M, 45)	25 mg (0.3 mg/kg)	-	25 mg (0.3 mg/kg)	IV bolus once	6 h	-

F: female; M: male; IV: intravenous; APs: antipsychotics; IM: intramuscular; BDZs: benzodiazepines.

TABLE 3. Cardiopulmonary effects of ketamine for agitation management (n = 20).

Case	Total ketamine dose (mg/kg)	Pre-RR	Post RR	Pre-OS	Post OS	Pre-HR	Post HR	Pre-SBP	Post-SBP
1	30 mg (0.4 mg/kg)	20	18	97%	100%	90	88	148	132
2	70 mg (1 mg/kg)	19	18	100%	100%	89	88	119	132
3	120 mg (2.2 mg/kg)	20	22	96%	100%	86	90	158	188
4	50 mg (0.7 mg/kg)	22	19	98%	98%	126	116	119	11
5	39.5 mg (0.5 mg/kg)	32	16	99%	100%	132	102	87	101
6	50 mg (0.5 mg/kg)	18	22	91%	96%	94	65	115	113
7	150 mg (1 mg/kg)	20	20	96%	96%	73	89	108	102
8*	50 mg (0.7 mg/kg)	24	16	68%	98%	106	63	145	104
9	25 mg (0.7 mg/kg)	20	22	98%	98%	72	70	118	117
10	50 mg (0.8 mg/kg)	20	20	98%	95%	82	80	121	121
11$^{\pi}$	35 mg (0.9 mg/kg)	23	22	100%	100%	139	133	90	92
12	40 mg (0.5 mg/kg)	20	19	97%	97%	83	81	101	112
13	25 mg (0.75 mg/kg)	24	23	97%	96%	75	75	125	122
14	40 mg (0.6 mg/kg)	26	23	98%	98%	110	103	150	134
15$^{\pi}$	25 mg (0.5 mg/kg)	20	20	98%	98%	82	79	102	102
16*	50 mg (0.5 mg/kg)	22	22	97%	96%	98	88	187	182
17	30 mg (0.5 mg/kg)	18	15	95%	98%	95	82	112	122
18*	50 mg (0.75 mg/kg)	14	16	98%	98%	110	92	179	172
19	25 mg (0.4 mg/kg)	20	20	99%	99%	96	74	134	122
20	25 mg (0.3 mg/kg)	23	19	98%	99%	108	89	153	132
Average difference (pre & post-therapy)		Decrease by 1.6 ± 2		Increase by 3% ± 0.1		Decrease by 8.5 ± 4.9		SBP Increase by 0.73 ± 6.3	

HR: heart rate; OS: oxygen saturation; RR: respiratory rate; SBP: systolic blood pressure.
** Elderly patients (#8: 71 years old; #16: 71 years old; #18: 66 years old).*
$^{\pi}$ Pediatric patients (#11: 7 years old; #15: 9 years old).

4. Discussion

Despite ketamine's safe usage for acute agitation in the ED, BDZs or APs, either the first or second generation, are the recommended agents [14, 17, 21–23]. Its pharmacokinetic properties such as the short duration of action that may necessitate additional calming drugs and its pharmacodynamic characteristics that may lead to an increase in BP, HR and salivation, the feeling of nausea or laryngospasm, and the belief of enhancing acute agitation in schizophrenia patients could make ketamine a less favorable drug for acute agitation management [8, 17, 20]. In all the EDs included in our study, only 21 subjects were administered ketamine for a definite diagnosis of acute agitation. Similarly, across 12 hospitals and 6 separate EDs in the United States between May 2017 and May 2018, ketamine was used only in 37 subjects with acute agitation [21]. However, its usage as an agitation controller in the ED has been assessed in several studies. In contrast to the ED, ketamine usage for managing agitation in the prehospital setting seems common, because attempting to handle the same severely agitated patients in the field with limited paramedic resources is considerably more challenging, and the urgency to gain control is heightened [16]. While waiting for 20 minutes for antipsychotics to take effect might be appropriate for the majority of patients in an emergency department, the threshold is lower for paramedics due to the increased risk in the field.

Of all our patients (n = 20) who were administered ketamine for acute agitation in the ED, only 6 (30%) patients needed additional calming medications. These patients presented to the ED with various complaints: behavioral/psychiatric changes (n = 3), multiple drug intoxication (n = 1), trauma post RTA (n = 1), and IHD (n = 1). In a similar study that included 32 agitated patients administered ketamine in the EDs of two academic hospitals in the United States, 65.5% of the subjects needed subsequent calming drugs [8]. An open-label randomized trial conducted in the ED of a tertiary hospital in

the United States compared the sedation achievement between ketamine (n = 44) and lorazepam/haloperidol (n = 49) among acute agitated patients and found that 22% of the ketamine group needed additional calming medications as opposed to 20% of the lorazepam/haloperidol group [17]. Additionally, the need for rescue medication was reported to be 58.3% (n = 14/24) in the ketamine group, 78.9% (n = 15/19) in the midazolam group, 78.8% (n = 26/33) in the lorazepam group, and 50% (n = 7/14) in the haloperidol group when these agents were compared in a prospective observational study on acute agitation management in the ED [20].

Most of the literature that studied ketamine for acute agitation management in EDs either assessed or proposed IM ketamine dose [19–21, 29]. Although 3–5 mg/kg of ketamine administered as IM injection is considered the usual dose, recent studies suggest a dose of 2, 3 or 4 mg/kg IM as the optimal, safest dose [19–21]. In contrast, most of our subjects were administered ketamine as an IV bolus (n = 19 out of 20). The dose range for the IV bolus ketamine in our subjects was between 0.3 and 2.2 mg/kg. The doses of 0.5 mg/kg and 0.7–0.8 mg/kg achieved 83.3% and 66.7% success rates respectively, while the low initial dose of 0.3 mg/kg was not effective. An almost similar dose range of 0.31–2.2 mg/kg of IV bolus ketamine (n = 18 of 24 in the ketamine group) was reported in a single-centered observation study for managing acute agitation in EDs, and ketamine, in general, showed better efficacy and safety over BDZs or APs [14]. However, there were no details of particular dose efficacy. In an open-label trial with the same aim, only 2 of the 44 patients in the ketamine group were administered ketamine as an IV bolus with a dose of 1 mg/kg, while the remaining took 4 mg/kg ketamine as IM [17]. Generally, ketamine as an initial calming medication in this trial achieved a significant faster sedated onset than the combination of lorazepam and haloperidol (66% *vs.* 7%, $p < 0.001$), but it was significantly associated with transient tachycardia (34% *vs.* 11%, $p = 0.014$) and hypertension (33% *vs.* 11%, $p = 0.012$). The common initial fixed dose of ketamine IV bolus in our study was 50 mg (n = 6 out of 19) with a success rate of 66.7% (4 out of 6). A seven-year chart review study at the EDs of two teaching hospitals was conducted to assess the efficacy and safety of ketamine as a medication for acute agitation [8]. A total of 32 patients were included, and 15 patients were administered ketamine as an IV bolus. Of those given ketamine as an IV bolus, the most common initial dose was 100 mg in 6 patients, three of whom did not need additional rescue medications. Unlike most pre-hospital studies that assessed ketamine for managing acute agitation using IM injection [30–34], one pre-hospital study assessed the efficacy and safety of IV ketamine for managing agitation among 21 patients during medical aviation [35]. A dose range of 0.5–2.7 mg/kg (median dose of 1.2 mg/kg/hr) for non-intubated patients and a dose range of 1.6–3 mg/kg (median dose of 2.8 mg/kg/hr) for intubated patients were reported. Of those, 10 patients were effectively administered only ketamine IV bolus with a dose range of 20–160 mg, while the others needed subsequent ketamine IV infusion.

Mostly, no clinically significance impacts of ketamine administration on the cardiac or respiratory markers were noted in our subjects. The average post-administration decrease of RR and HR were 1.6 ± 2 breaths/min and 8.5 ± 4.9 beats/min respectively, while the average post-administration increase of OS was 3% ± 0.1%. Regarding the SBP, there was a very slight post-administration increase of 0.73 ± 6.3 mmHg. The concern increased in the SBP was seen in two cases who received a total IV dose of ≥1 mg/kg or >50 mg. A similar study (n = 32) in EDs showed an average non-clinically significant increase of 17 ± 25 mm Hg in SBP and an increase of 8 ± 17 beats/min 4 hours after ketamine administration for acute agitation [8]. It also showed an average increase of 1.1 ± 1.7% in OS, with no cases of hypoxia. A study comparing ketamine (n = 44) and lorazepam plus haloperidol (n = 49) for acute agitation management in ED found that ketamine was statistically associated with hypertension (SBP or DBP increase of ≥20 mmHg; $p = 0.012$) and tachycardia (HR increase of ≥10 beats/min; $p = 0.014$) [17]. The used dose of ketamine in this study was 4 mg/kg IM (n = 42) and 1 mg/kg IV (n = 2).

Our study is limited by the small sample size that required the cases series description and does not allow the statistical, inferential or clinical generalization of data. The rare clinical usage of ketamine as a calming agent for acute agitation in EDs, the strict inclusion criteria of including only patients who were started on ketamine as an initial calming drug, and poor documentation in hectic environments such EDs could contribute to the small sample size. The retrospective chart review method of study with a single-armed group is another limitation.

5. Conclusions

Our study found that ketamine is seldom used as an initial medication for acute agitation in the ED. A starting dose of 0.5–1 mg/kg or 50 mg of ketamine as an IV bolus injection showed reasonable effectiveness and appropriate safest properties to calm our agitated patients in EDs.

ABBREVIATIONS

APs, Antipsychotics; ED, Emergency Department; BDZs, Benzodiazepines; HR, Heart Rate; IM, Intramuscular; IV, Intravenous; OS, Oxygen Saturation; BP, Blood Pressure; RR, Respiratory Rate; SBP, Systolic Blood Pressure.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

SuA and SaA—Conceptualization, Visualization and supervision; SuA and AA—Methodology, Writing, reviewing and editing; AA—Formal analysis; GAA, RA and MAK—Investigation; GAA and RA—Original draft preparation.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Review Board (IRB) at both (1) King Saud University Medical Center (KSUMC) (Ref. No. 22/0409/IRB) and (2) Al-Habib Medical Group (HMG) (Ref. No. RC22.12.3). Since this study is a retrospective observation study without intervention, the subject consent form was waived by the IRBs of involved hospitals.

ACKNOWLEDGMENT

The authors extended their appreciation to the Deputyship for Research and Innovation, "Ministry of Education" in Saudi Arabia for funding this research (IFKSUOR3-620-1).

FUNDING

This research was funded by the Deputyship for Research and Innovation, "Ministry of Education" in Saudi Arabia (IFKSUOR3-620-1).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Gonin P, Beysard N, Yersin B, Carron P. Excited delirium: a systematic review. Academic Emergency Medicine. 2017; 25: 552–565.

[2] Knott JC, Bennett D, Rawet J, Taylor DM. Epidemiology of unarmed threats in the emergency department. Emergency Medicine Australasia. 2005; 17: 351–358.

[3] Tadros A, Kiefer C. Violence in the emergency department. Psychiatric Clinics of North America. 2017; 40: 575–584.

[4] American College of Emergency Physicians Excited Delirium Task Force. White paper report on excited delirium syndrome. 2009. Available at: https://www.prisonlegalnews.org/media/publications/acep_report_on_excited_delirium_syndrome_sept_2009.pdf (Accessed: 02 July 2023).

[5] Vilke GM, Payne-James J, Karch SB. Excited delirium syndrome (ExDS): redefining an old diagnosis. Journal of Forensic and Legal Medicine. 2012; 19: 7–11.

[6] Lipsedge M. Excited delirium: a psychiatric review. Medicine, Science and the Law. 2016; 56: 121–127.

[7] Wong AH, Ray JM, Cramer LD, Brashear TK, Eixenberger C, McVaney C, *et al*. Design and implementation of an agitation code response team in the emergency department. Annals of Emergency Medicine. 2022; 79: 453–464.

[8] Hopper AB, Vilke GM, Castillo EM, Campillo A, Davie T, Wilson MP. Ketamine use for acute agitation in the emergency department. The Journal of Emergency Medicine. 2015; 48: 712–719.

[9] Jamal SM, Fathil SM, Nidzwani MM, Ismail AK, Yatim FM. Intravenous ketamine is as effective as midazolam/fentanyl for procedural sedation and analgesia in the emergency department. The Medical journal of Malaysia. 2011; 66: 231–233.

[10] Sih K, Campbell SG, Talion JM, Magee K, Zed PJ. Ketamine in adult emergency medicine: controversies and recent advances. Annals of Pharmacotherapy. 2011; 45: 1525–1534.

[11] Burnett A, Panchal D, Peterson B, Ernest E, Griffith K, Frascone RJ, *et al*. The administration of prehospital ketamine for chemical restraint does not prolong on-scene times compared to Haloperidol based sedation. Australasian Journal of Paramedicine. 2015; 12: 1–7.

[12] Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Annals of Emergency Medicine. 2011; 57: 449–461.

[13] Goddard K, Sampson C, Bedy S, Ghadban R, Stilley J. Effect of ketamine on cardiovascular function during procedural sedation of adults. Cureus. 2021; 13: e14228.

[14] Riddell J, Tran A, Bengiamin R, Hendey GW, Armenian P. Ketamine as a first-line treatment for severely agitated emergency department patients. The American Journal of Emergency Medicine. 2017; 35: 1000–1004.

[15] Kurdi M, Theerth K, Deva R. Ketamine: current applications in anesthesia, pain, and critical care. Anesthesia: Essays and Researches. 2014; 8: 283.

[16] Sullivan N, Chen C, Siegel R, Ma Y, Pourmand A, Montano N, *et al*. Ketamine for emergency sedation of agitated patients: a systematic review and meta-analysis. The American Journal of Emergency Medicine. 2020; 38: 655–661.

[17] Lin J, Figuerado Y, Montgomery A, Lee J, Cannis M, Norton VC, *et al*. Efficacy of ketamine for initial control of acute agitation in the emergency department: a randomized study. The American Journal of Emergency Medicine. 2021; 44: 306–311.

[18] Sheikh S, Hendry P. The expanding role of ketamine in the emergency department. Drugs. 2018; 78: 727–735.

[19] Kim HK, Leonard JB, Corwell BN, Connors NJ. Safety and efficacy of pharmacologic agents used for rapid tranquilization of emergency department patients with acute agitation or excited delirium. Expert Opinion on Drug Safety. 2021; 20: 123–138.

[20] Gottlieb M, Long B, Koyfman A. Approach to the agitated emergency department patient. The Journal of Emergency Medicine. 2018; 54: 447–457.

[21] Mo H, Campbell MJ, Fertel BS, Lam SW, Wells EJ, Casserly E, *et al*. Ketamine safety and use in the emergency department for pain and agitation/delirium: a health system experience. Western Journal of Emergency Medicine. 2020; 21: 272–281.

[22] Yildiz A. Pharmacological management of agitation in emergency settings. Emergency Medicine Journal. 2003; 20: 339–346.

[23] Wilson M, Pepper D, Currier G, Holloman G, Feifel D. The psychopharmacology of agitation: consensus statement of the American Association for emergency psychiatry project BETA psychopharmacology workgroup. Western Journal of Emergency Medicine. 2012; 13: 26–34.

[24] Barbic D, Andolfatto G, Grunau B, Scheuermeyer FX, Macewan B, Qian H, *et al*. Rapid agitation control with ketamine in the emergency department: a blinded, randomized controlled trial. Annals of Emergency Medicine. 2021; 78: 788–795.

[25] Roppolo LP, Morris DW, Khan F, Downs R, Metzger J, Carder T, *et al*. Improving the management of acutely agitated patients in the emergency department through implementation of Project BETA (Best Practices in the Evaluation and Treatment of Agitation). Journal of the American College of Emergency Physicians Open. 2020; 1: 898–907.

[26] O'Brien ME, Fuh L, Raja AS, White BA, Yun BJ, Hayes BD. Reduced-dose intramuscular ketamine for severe agitation in an academic emergency department. Clinical Toxicology. 2020; 58: 294–298.

[27] Aghili M, AkhavanHejazi H, Naderpour Z, Vahidi E, Saeedi M. Haloperidol-Midazolam *vs.* Haloperidol-Ketamine in controlling the agitation of delirious patients; a randomized clinical trial. Archives of Academic Emergency Medicine. 2023; 11: e61.

[28] Szarmach J, Cubała WJ, Włodarczyk A, Wiglusz MS. Short-term ketamine administration in treatment-resistant depression: focus on cardiovascular safety. Psychiatria Danubina. 2019; 31: 585–590.

[29] 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. Bulletin of Emergency and Trauma. 2018; 6: 292–299.

[30] 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 Emergency Care. 2015; 19: 110–115.

[31] Cole JB, Klein LR, Nystrom PC, Moore JC, Driver BE, Fryza BJ, *et al*. A prospective study of ketamine as primary therapy for prehospital profound agitation. The American Journal of Emergency Medicine. 2018; 36: 789–796.

[32] Isbister GK, Calver LA, Downes MA, Page CB. Ketamine as rescue

treatment for difficult-to-sedate severe acute behavioral disturbance in the emergency department. Annals of Emergency Medicine. 2016; 67: 581–587.e1.

[33] Scheppke K, Braghiroli J, Shalaby M, Chait R. Prehospital use of IM ketamine for sedation of violent and agitated patients. Western Journal of Emergency Medicine. 2014; 15: 736–741.

[34] Hollis GJ, Keene TM, Ardlie RM, Caldicott DG, Stapleton SG. Prehospital ketamine use by paramedics in the Australian Capital Territory: a 12 month retrospective analysis. Emergency Medicine Australasia. 2017; 29: 89–95.

[35] Gangathimmaiah V, Le Cong M, Wilson M, Hooper K, Perry A, Burman L, *et al*. Ketamine sedation for patients with acute behavioral disturbance during aeromedical retrieval: a retrospective chart review. Air Medical Journal. 2017; 36: 311–314.

How to cite this article: Sultan Alghadeer, Ghadeer A. Alhamid, Rana Almotawa, Abeer Alshareef, Mohmad A. Knas, Saqer Althunayyan. The Effective dose of ketamine in the management of acute agitation in emergency departments. Signa Vitae. 2024. doi: 10.22514/sv.2024.066.