Effect of Intramuscular Ketamine versus Haloperidol on Short-Term Control of Severe Agitated Patients in Emergency Department; A Randomized Clinical Trial

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> ABSTRACT

Objective: To evaluate the efficacy and safety of intramuscular ketamine and haloperidol in sedation of severely agitated patients in emergency department (ED).
Methods: This randomized, double-blind clinical trial study was performed on agitated patients referring to two university educational hospitals. Patients were randomly assigned to receive intramuscular (IM) haloperidol (5 mg) or IM ketamine (4 mg/kg). The primary outcome was time to adequate sedation (AMSS≤+1). Secondary outcomes included the need for additional sedatives, required intubation, duration of hospitalization, and side effects.
Results: The 90 agitated patients were enrolled. The mean age was 30.37±7.36 years (range 18–56); 74% (67/90) were men. The mean time to adequate sedation in ketamine group (7.73±4.71 minutes) was significantly lower than haloperidol group (11.42±7.20 minutes) (p=0.005). 15 minutes after intervention, the sedation score did not differ significantly in both groups (Ketamine: 0.14±0.59 vs. Haloperidol: 0.30±0.60; p=0.167). The incidence of complications was not significantly different between groups. The physician's satisfaction from the patients' aggression control was significantly higher in ketamine group.
Conclusion: These data suggest ketamine may be used for short-term control of agitated patients, additional studies are needed to confirm if ketamine is safe in this patient population. Given rapid effective sedation and the higher physician satisfaction of ketamine in comparison to haloperidol, it may be considered as a safe and appropriate alternative to haloperidol.
Trial registration number: IRCT20180129038549N5

Keywords: Psychomotor agitation; Emergencies; Haloperidol; Ketamine; Aggitation.

Introduction

Agitated, violent, psychotic, and behaviorally disturbed patients are a common presentation to the emergency department (ED) [1,2]. The control of agitated and aggressive patients who present a danger to themselves and hospital personnel is a major problem for healthcare workers in the EDs [2,3]. Several underlying etiologies including medical and psychiatric disorders can manifest as agitation. Agitation and behavioral disturbance are also frequently seen in Substance and alcohol use [2-4]. Agitated patients may respond to verbal de-escalation as first-line treatment [4,5]. When these techniques are insufficient, physical or pharmacological restraint may be necessary. Of the two methods, pharmacological restraint is safer and the more humane option [2]. Chemical sedation may be required to prevent injuries to patients and staff, and to allow the clinician to assess these patients for safe and effective medical evaluation and treatment [2-5]. Medications are used which have the quick effect and least complications. Sedative and anesthetic drugs have long been used in the pre-hospital emergency protocol. Currently, the most commonly used agents are antipsychotics and benzodiazepines; a combination of the 2 classes has also become a popular regimen in managing agitation [2,3].

To date, a wide range of regimens has been used, mostly including benzodiazepines (diazepam, midazolam, and lorazepam), first generation antipsychotic (chlorpromazine, haloperidol, droperidol), second generation antipsychotic (ziprasidone, loxapine, olanzapine), combination of these (e.g., lorazepam in combination with haloperidol), and Ketamine [2-11], administered by either the intramuscular or intravenous route, and they have been introduced as safe and applicable drugs for agitation control in aggressive patients. Ketamine is a fast-acting, safe and effective medication in agitated and violent patients with a low rate of side effects in the prehospital setting [1,12,13] and as a rescue medication in patients who failed previous sedation attempts in ED [3]. Little published research has been done on the effectiveness of ketamine for the first line treatment of agitated patients in the EDs [3-5]. However, there is limited information regarding comparison of the effectiveness of these drugs as the quickest effect and least possible complications. The goal of the current study was to compare the effectiveness and safety of intramuscular (IM) ketamine and Haloperidol in severely agitated and aggressive patients in the ED. The primary outcome was time to adequate sedation (AMSS≤+1). The secondary outcomes included the need for additional sedatives, required intubation, duration of hospitalization, and side effects.

Materials and Methods

Study Design and Setting

This was a prospective, randomized, double-blinded clinical trial examining agitated and violent ED patients requiring medication for sedation. The study was conducted in the adult ED of Al-Zahra and Kashani Hospitals, two university educational hospitals, affiliated with Isfahan University of Medical Sciences in Iran from January 2015 to March 2016. This study was approved by the ethics committee of Isfahan University of Medical Sciences (IR.MUI.REC. 1395.3.661). The trial was registered in the Iranian Registry of Clinical Trials under the number (IRCT20180129038549N5).

Selection of Participants

The patients with acute agitated and aggressive behavior between the ages of 17 and 65 who required chemical sedation for agitation, according to an emergency medicine resident or attending physician were eligible for enrollment. The altered mental status score (AMSS) was used as an agitation measurement tool [14,15]. This scale is a modified version of the Behavioral Activity Rating Scale with additional data points from the Observer's Assessment of Alertness Scale [16]. Because the AMSS provides information on both the degree of agitation and the depth of sedation, it can be used to determine the time to adequate sedation (Table 1). Severe agitation was defined by all agitated, aggressive, destructive, assaultive, and restless behavior patients, that is, generally all the patients who intended to damage themselves or others with an AMSS score of +2 or +3 [14]. Patients with profound agitation (AMSS score of +4) because of it would be unethical to withhold ketamine treatment to these patients and patients who could be settled (AMSS≤1) with verbal de-escalation were excluded. It should be noted that Ketamine and Haloperidol contraindications, pregnancy, prisoners, persons in police custody and treatment with a benzodiazepine or neuroleptic within the previous 24 hours were considered as the exclusion criteria for the study.

Study Protocol

All patients with severe agitation (AMSS +2 or +3) were randomly allocated to two groups A and B (n=45) using a computer-generated random number table to ensure roughly equal numbers in each group. A nurse not involved with patient enrollment, data collection, or data analysis conducted the randomization with random number tables and kept the codes confidential. Patients did not have a companion to provide consent and required immediate sedation for patient and staff safety, consent was waived because medical treatment was provided as a duty of care. Due to the observational nature of this study, medication dosages were not uniform. Current published dosage recommendations for these medications include ketamine 4 – 6 mg/kg intramuscular (IM) [17], haloperidol 5 -10 mg IM [2,8]. In order to observe double-blindness of the study, firstly the solutions were daily prepared,

Table 1. Altered mental status scale (AMSS).

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

recorded, and marked by the pharmacist (without awareness of the authors). Solution A contained 5 mg of Haloperidol (5 mg/ml, made in Kimia Daroo Co.) and solution B contained 4 mg/kg (dose calculation made by estimated weight) of Ketamine (50 mg/ml, made in ROTEXMEDICA Co.) (3). The two solutions were then given to the emergency department nurse, according to the allocation the solutions were injected intramuscularly to the patients. AMSS scores were recorded at time=0 and every 5 min after medication administration until adequate sedation was achieved. Providers also recorded the time at which they thought adequate sedation (primary outcome) had been achieved. Time to adequate sedation was defined as the time from medications administration until the patient achieved an AMSS score ≤+1. In addition, demographic and clinical characteristics such as age and sex, vital signs such as blood pressure, pulse rate, respiration rate, possible causes of the agitated and aggressive behavior (traumatic-psychotic-abuse), side effects such as hypoxia, increase or decrease in blood pressure and pulse rate, nausea and vomiting, need for intubation (if refractory agitation, Hypersalivation, Respiratory failure or Laryngospasm,..), and extrapyramidal complications were recorded in the checklist for each patient. Sixty minutes after the first injection (T60), physician's satisfaction regarding agitation control (excellent, good, moderate, or weak) was recorded. The answers of excellent and very good were supposed as reaching proper agitation control.

Interventions

All the included patients were randomly assigned into to two study groups, every with45 patients. The first group (ketamine group) received ketamine 4mg/kg IM and the second group (haloperidol group) received haloperidol 5mg IM. The medications were administered IM by a nurse who was blind to the study protocol. Adequate sedation was obtained as defined by an AMSS score not exceeding 1. In case of not achieved adequate sedation or required additional sedation, according to the physician's opinion, the second dose was injected with half the initial dose of the same medication. If agitation was not yet controlled by the second dose, then Midazolam (2 to 2.5 mg/kg) was administered intravenously [2,13], and these cases were also recorded. The use of second dose and additional medication (midazolam) were recorded.

Statistical Analysis

The collected data were entered in statistical package for social sciences (SPSS Inc., Chicago, Illinois, USA) Software (Ver. 20) and given results of Kolmogorov Smirnov test on the normal distribution of quantitative data, parametric tests such as independent t-test, General Linear Model and repeated measures ANOVA were used. Chi-square test and Fisher's exact test were used for comparing qualitative data between two groups. Moreover, all analysis was considered as significance level smaller than 0.05.

Results

The 90 agitated patients, between January 01, 2015 to March 30, 2016, were enrolled (Figure 1). The mean age was 30.37±7.36 years (range 18 –56); 74% (67/90) were male. In the Ketamine group, 33 (73.3%) were males and 12 (26.7%) were females with mean age of 30.80±7.73 years, and in the Haloperidol group, 34 (75.6%) were males and 11 (24.4%) were females with a mean age of 29.93±7.91 years. There was no difference between the groups in terms of demographic characteristics (p>0.05). There were no significant differences based on the cause of aggressive behavior, respiratory rate, pulse rate, blood pressure (SBP) and O_2 saturation (Table 2). Patients' demographic and clinical characteristics are shown in Table 2.

There was no significant difference between groups in initial agitation scores (Table 3). Based on agitation
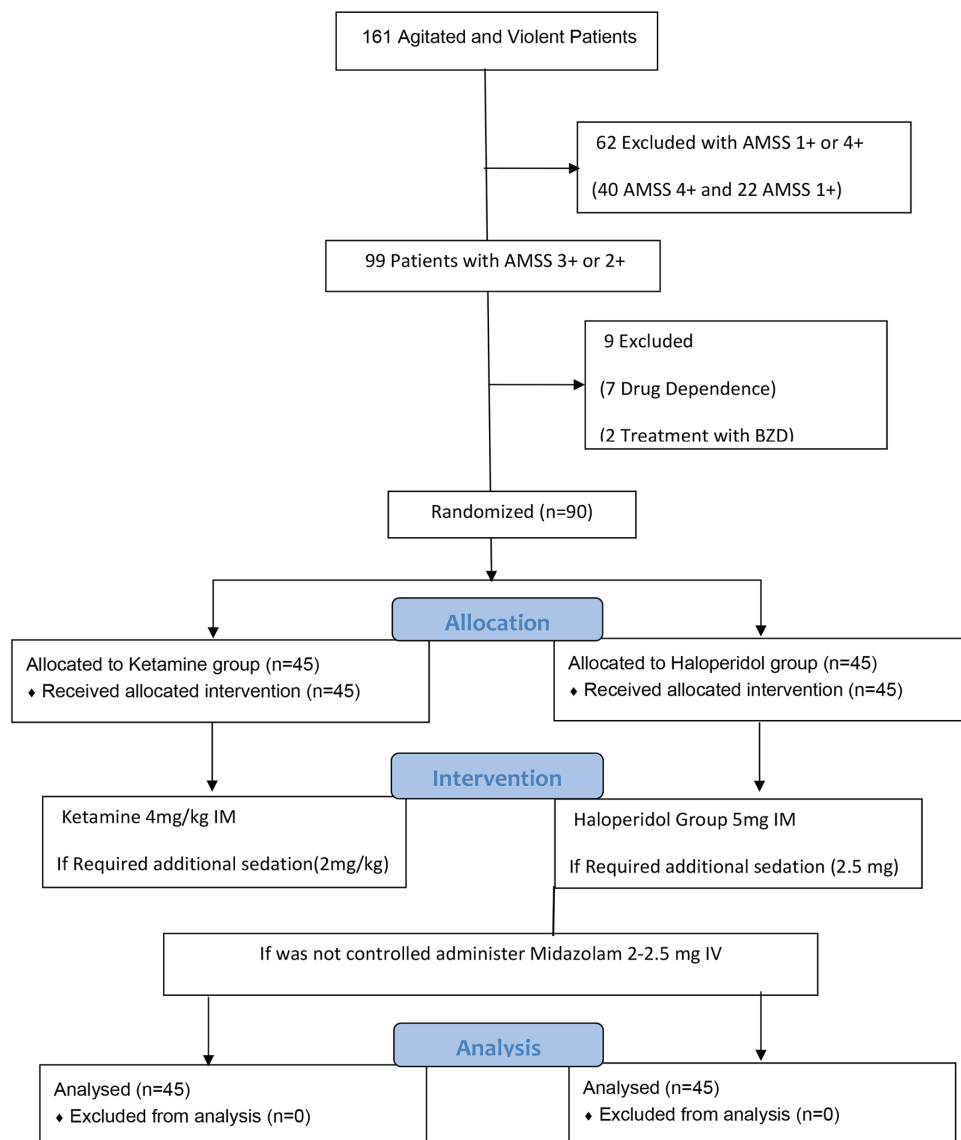
Fig. 1. CONSORT flow diagram of the study.

Table 2. Basic and clinical characteristics of patients in the two groups.

Characteristics		Ketamine (n=45)	Haloperidol (n=45)	*p* value
Age (years)		30.80±7.73	29.13±7.91	0.315
Sex	Male	33 (73.3%)	34 (75.6%)	0.809
	Female	12 (26.7%)	11 (24.4%)	
Cause of aggressive behavior	Psychotropic Substances	12 (26.7%)	12 (26.7%)	0.831
	Psychiatric History	13 (28.9%)	15 (33.3%)	
	Alcohol Consumption	12 (26.7%)	13 (28.9%)	
	Trauma	8 (17.8%)	5 (11.1%)	
Vital signs	Respiratory Rate; per minute	18.13±2.53	18.53±2.63	0.464
	Heart Rate; beats per minute	83.53±12.81	83.24±14.04	0.289
	Systolic Blood Pressure; mmHg	119.20±17.20	120.80±16.73	0.656
	O$_2$ saturation; %	97.29±2.15	97.27±1.89	0.959

scores at 5 minutes (T5) after receiving medication, there was no significant difference between groups. After 10 minutes (T10), agitation scores (AMSS score) in ketamine group was significantly lower than the haloperidol group (*p*-value=0.001), although there was no significant difference in the AMSS score between the two groups at 15 minutes (T15) after. Also, by controlling confounding factors such as injection a repeat dose of medication or an additional midazolam, the significant difference between the two groups at 10 minutes after the intervention was still remained (Table 3).

Table 3. Determination and comparison of AMSS scores of patients at the admission time,5, 10 and 15 minutes after intervention in two groups.

	Time(min)	Ketamine (n=45)	Haloperidol (n=45)	*p* value	
				Unadjusted[a]	Adjusted[b]
Score of AMSS	0	2.62±0.94	2.59±1.13	0.918	0.917
	5	1.36±1.01	1.70±1.07	0.134	0.115
	10	0.67±0.19	1.27±0.81	0.001	0.001
	15	0.14±0.59	0.30±0.60	0.180	0.167
p value[c]		<0.001	<0.001		

[a]Comparison Mean AMSS score between two groups using Independent sample test; [b]Comparison Mean AMSS score between two groups using GLM test by adjusted for repeat dose of midazolam; [c]Comparison the mean of AMSS scores over time from the time of admission up to 15 minutes after intervention in each group

The primary outcome was time to adequate sedation (AMSS≤+1). Median time to adequate sedation was 7.7 min (95% confidence interval [CI]: 5.2–9.9, range 1–20 min) and 11.4 min (95% CI: 8.5–13.9, range 3–34 min) in ketamine group and haloperidol group, respectively. It was found that this time in ketamine group was significantly lower than haloperidol group ($p<0.01$, difference 3.7 minutes, 95% CI: 2.1–5.5). Based on agitation scores at T15 after receiving medication, adequate sedation was achieved in 82% (74/90) of patients. Adequate sedation at T15 was not achieved in 13 (28.9%) and 3 (6.7%) in haloperidol and ketamine groups, more patients in the ketamine group were no longer agitated than the haloperidol group in these time ($p<0.0001$, difference 0.22, 95% CI 0.11–0.33).

Based on results, 64.4% of patients who received Ketamine and 51.1% of patients in Haloperidol group required repeated dose (half of the initial dose) ($p=0.289$, difference 0.13, 95% CI 0.07–0.18), and 24.4% of the patients in Ketamine group and 17.8% of the patients in Haloperidol group required additional drugs. There was no significant difference between groups in the requirement for repeated doses or additional medication (Table 4). The incidence of complications was 17.8% for haloperidol and 35.6% for ketamine, there was no significant difference between groups ($p=0.094$, difference 0.17, 95% CI 0.11–0.22). Complications included hypersalivation (n=5, 11.1%), vomiting (n=6, 13.3%), Laryngospasm

(n=2, 4.4%), and emergence phenomena (n=3, 6.7%) in ketamine group and vomiting (n=1, 2.2%), dystonia (n=2, 4.4%), akathisia (n=4, 8.9%), and hypoxia (n=1, 2.2%) in haloperidol group.

Intubation occurred in 6(13.3%), and 3(6.7%) of patients in ketamine and haloperidol group, there was no significant difference between groups ($p=0.485$). Primary indications for intubation, were refractory agitation (n=1), hypersalivation (n=2), and hypoxia (n=3) in ketamine group and refractory agitation (n=2), hypoxia (n=1) in haloperidol group. All9 patients who underwent intubation were given an additional medication (midazolam). A total of, 36 physicians (80.0%) in the ketamine group and 26 patients (57.8%) in the haloperidol group were satisfied with the agitation control (excellent and good). Satisfaction of physicians was significantly different between the two groups ($p=0.011$) (Table 4).

Discussion

The aim of the current study was to compare the effectiveness and safety of intramuscular (IM) ketamine and Haloperidol in 90 severely agitated and aggressive (AMSS scores +2 and +3) patients in the ED; Ketamine was more successful in the initial sedation than Haloperidol. The median time to adequate sedation was about 8 minutes in ketamine group while this time for Haloperidol group was about 12 minutes.

Table 4. Determination and comparison of the frequency distribution of patients' conditions after sedation and physicians' satisfaction in the two groups.

Variables		Ketamine (n=45)	Haloperidol (n=45)	*p* value
Repeat dose	No	16 (35.6%)	22 (48.9%)	0.289
	Yes	29 (64.4%)	3 (51.1%)	
Additional Drug (Midazolam)	No	34 (75.6%)	37 (82.2%)	0.606
	Yes	11 (24.4%)	8 (17.8%)	
Incidence of complications	No	29 (64.4%)	37 (82.2%)	0.094
	Yes	16 (35.6%)	8 (17.8%)	
Satisfaction	Weak	1 (2.2%)	2 (4.4%)	0.011
	Moderate	8 (17.8%)	17 (37.8%)	
	Good	10 (22.2%)	21 (46.7%)	
	Excellent	26 (57.8%)	5 (11.1%)	
Intubation	No	39 (86.7%)	42 (93.3%)	0.485
	Yes	6 (13.3%)	3 (6.7%)	

Cole et al. concluded that ketamine was superior to haloperidol in terms of time to adequate sedation for severe prehospital acute undifferentiated agitation, but was associated with more complications and a higher intubation rate [1]. The median time to adequate sedation was 5 minutes with ketamine that is consistent with both procedural sedation literature as well as retrospective data on patients with prehospital acute undifferentiated agitation [1,17,18]. The haloperidol median time to adequate sedation is 12 minutes which is similar to previously published work both in the prehospital environment and emergency department [1,3,19]. Nobay *et al.* showed longer time to adequate sedation after haloperidol administration [20]. The mean±SD time to sedation was 28.3±25 minutes. This difference may be due to different scale used to assess the adequate sedation, also the end point for time to sedation varied between the studies and was reported in various formats. Ketamine has been used to control of agitation in the prehospital, aeromedical, military, and ED settings [1,5,13,14,21]. Contrary to our study, Isbister *et al.* was showed that the median time to sedation after ketamine administration was 20 minutes, and they concluded that Ketamine appears to be less effective and third-line agent in the sedation of patients with acute behavioral [4]. Riddell *et al.* showed that, in highly agitated and violent emergency department patients, significantly fewer patients receiving ketamine as a first line sedating agent were agitated at 5-, 10-, and 15-min. Ketamine appears to be faster at controlling agitation than standard ED medications [3].

Haloperidol has been used effectively for many years to control violent and agitated patients. It can be given IV, IM, or orally, although its IV use is not approved by the US Food and Drug Administration (FDA). Droperidol and olanzapine can be given IM or IV [10,22]. A prospective observational study of 784 patients presenting to the emergency department for a variety of conditions reported that both IM and IV olanzapine provided adequate sedation [22].

In this study, 64.4% of patients who received Ketamine and 51.1% of patients in Haloperidol group required repeated dose (half of the initial dose), and 24.4% of the patients in Ketamine group and 17.8% of the patients in Haloperidol group required additional drugs (midazolam 2-2.5 mg/kg). Cole *et al.*, [1] reported that five percent of patients in ketamine group (3/64) required additional sedation prehospital whereas20% of patients in haloperidol group required a second injection prehospital.

Also in previous studies, 62.5% of patients required additional sedating medication [5] or 58.3 % of them needed to repeat the dose of Ketamine [3]. They said that, high proportion (62.5%) of patients required additional pharmacologic treatment for agitation, implying that administering ketamine is useful only for initial control of severe agitation. However, there was no significant difference between the groups in terms of re-administration of doses and additional drugs. In the present study, the incidence of complications was 17.8% for haloperidol and35.6% for ketamine, there was no significant difference between groups, but the type of complications was different. In Ketamine group, the patients had vomiting, hypersalivation, emergence phenomenon, and laryngospasm. In contrast to Haloperidol group had dystonia, akathisia, vomiting, and hypoxia. According to previous studies, the Haloperidol complications include mainly extrapyramidal dystonic reactions. Patients between 16 and 60 years are susceptible to Akathesia.

In contrast with our study, it has reported that the complication rate was significantly higher in ketamine group as 49% of patients receiving ketamine vs. 5% (4.82) in the haloperidol group [1]. Cole *et al.*, [1] demonstrated that laryngospasm occurred in 5% of patients receiving ketamine, much higher than the 0.3% rate was typically found in procedural sedation patients. Of course given that laryngospasm and emergence phenomenon were assessed for based upon clinical definitions and experience and may have been less accurately diagnosed. Similar to previous literature vomiting occurred at the rate of 9% in ketamine group [23]. Due to ketamine's mechanism of action, the occurrence of akathisia and dystonia in patients who received ketamine is unexpected, however, in a partially dissociated state, it is possible these complications remained unrecognized emergence reactions that occurred in 10% of patients receiving ketamine which is also similar to previous literature [24].

In addition, 13.3% of the patients in Ketamine group and 6.7% in Haloperidol group needed intubation. However, the intubation rate was twice as common with ketamine as haloperidol but, we did not have enough patients to make a conclusion about this differences. In another study it has been reported that intubation rate was significantly higher in ketamine group as 39% of patients receiving ketamine were intubated vs. 4% of patients receiving haloperidol [1]. Riddell *et al.*, [3] showed that only2/23 (8.7%) of ketamine patients were intubated. Olives *et al.*, [25] showed that endotracheal intubation was undertaken for 63% (85/135) of patients, including attempted prehospital intubation in four cases. In contrast, in a retrospective study, none of the patients who received emergency treatment to control their agitation needed intubation [5]. Scheppke *et al.*, [13] observed a very low intubation rate of 4% in a retrospective series of 52 patients receiving 4 mg/kg of IM ketamine for prehospital agitation. The physician's satisfaction was significantly higher in Ketamine group than Haloperidol group. This could be due to sedation and faster control of the agitated patients and exposure to less harmful complications compared to Haloperidol.

One of the limitations of the study was the sample size; although Ketamine has the same adverse effects

as other home remedies. Ketamine administration was associated with no serious adverse events, larger sample s would be required to reliably confirm its safety profile. Also, the used doses were not uniform and are different according to the types of drugs. However, the average dose of drugs used was less than the recommended dose for Ketamine, Haloperidol, and midazolam, and the cautious were observed in this regard. This study was not powered to detect differences in some adverse events like intubation. We also did not account for pre-hospital treatment. It may be possible that some patients received medication prior to presenting to the ED. Lack of validation of physician satisfaction is a limitation of our study. A patient's weight is not routinely included in ED charts, and so precludes further evaluation of the appropriateness of dosing in most cases.

In conclusion, relative to other pharmacologic treatments for agitation, ketamine is infrequently used in the ED. In summary, ketamine administered at 4 mg/kg IM provided rapid sedation (median time to adequate sedation 7.8 min) to patients with severe agitation (AMSS +2 or +3) in the ED. These data suggest ketamine may be used for short-term control of agitated patients, additional studies are needed to confirm if ketamine is safe in this patient population. In addition, given rapid effective sedation and the higher physician satisfaction of ketamine in comparison to haloperidol, this drug may be considered as a safe and appropriate alternative to haloperidol.

Acknowledgment

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