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The use of intramuscular ketamine by paramedics in the management of the severely agitated patient.

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SB and KS conceived the study and design. AD and RR collected and reviewed the pre-hospital data. RR co-ordinated the hospital data collection with the study investigators and completed the analysis. SB, KS, RR and AD contributed to the data interpretation. The first draft of the manuscript was written by SB, RR and AD, and all authors and the study investigators contributed and approved the final manuscript.

Conflict of interest statement

None declared.

Abstract

Objectives: Administration of a sedative agent is required for safe transport of prehospital patients with severe agitation to emergency departments (ED). Ambulance services in Australasia use ketamine, droperidol or midazolam as first line agents but the optimal agent is uncertain. In Victoria, intramuscular (IM) ketamine is used. This study aimed to examine the prehospital characteristics and ED outcomes of patients with severe agitation after IM ketamine administration.

Methods: A retrospective review was conducted for patients who received IM ketamine for severe agitation over a two year period. Data were sourced from Ambulance Victoria and linked to hospital data. The primary outcome was time to sedation. Data collected included baseline characteristics, adverse events and ED outcomes.

Results: 358 prehospital cases transported to 32 hospitals were included. Outcome data were available for 305 patients (21 hospitals). Median age was 31 years (IQR 23.0, 40.0). 71.2% were male. Adequate sedation was achieved in 96.9% of cases in a median time of 5.0 minutes (IQR 3.0, 7.0: Range 1-31 minutes). Adverse events were transient hypoxia (5.0%), hyper-salivation (4.2%) and emergence reactions (0.8%). A total of 45 (14.8%) patients were intubated; two prehospital.

Conclusion: Intramuscular ketamine is effective with a low rate of pre-hospital complications in severely agitated patients in the prehospital setting. Given the variation in ambulance practice in Australasia, prospective, randomised trials in the prehospital setting comparing ketamine to other sedating agents such as droperidol in patients with severe agitation are required.

Keywords:
Ketamine
Agitation
Ambulance
Emergency Department
Intubation

Introduction

Ambulance services in Australasia regularly encounter agitated patients due to mental illness and/or drug or alcohol intoxication. Whilst mild agitation may be responsive to verbal de-escalation techniques[1], severe agitation will require chemical restraint to facilitate safe transport to the emergency department (ED). In addition to the significant safety threat to themselves and attending police and paramedics, patients with severe agitation following amphetamine overdose are at risk of developing hyper-adrenergic autonomic dysfunction which carries a high rate of morbidity and mortality.[2]

The optimal choice of sedative to facilitate safe transport of these patients to the ED remains uncertain. Since intravenous (IV) cannulation is difficult in uncooperative patients, intramuscular (IM) options are required. In the 10 ambulance services in Australasia, four services use IM midazolam, three use IM droperidol and three use IM ketamine as the initial sedating drug in patients with severe agitation[3].

There have been previous reports on the use of benzodiazepines and/or anti-psychotics such as droperidol or haloperidol.[4,5,6] The use of ketamine in this setting has also been described in a recent meta-analysis.[7] This meta-analysis included one randomised trial comparing IM ketamine to IM haloperidol[8] and a number of case series describing IM ketamine use in the prehospital and ED settings.[9-11] Ketamine when administered IM has a rapid onset whilst maintaining airway reflexes, spontaneous respiration and hemodynamic stability. However, ketamine also has potential disadvantages including excessive salivation, hypertension, emergence reactions and laryngospasm. In Victoria, paramedics have administered 4mg/kg of IM ketamine for severe agitation since mid-2015. In this study, we sought to describe the characteristics, effectiveness and prehospital complications of patients who received IM ketamine for severe agitation due to mental illness and/or drug or alcohol intoxication in the prehospital setting. We also examined the emergency department management.

Methods

Study design

A retrospective review of medical records was performed in all patients who received IM ketamine for severe agitation due to suspected mental illness and/or drug or alcohol intoxication between 12th November 2015 and the 12th November 2017. Patients who received IM ketamine for agitation prior to planned intubation for traumatic brain injury or for pain relief following trauma were excluded from the analysis.

Setting

Ambulance Victoria is the sole emergency service provider for the state of Victoria, Australia servicing a population of more than 6.1 million people over 227,000 square kilometres. This service includes Advanced Life Support (ALS) and Intensive Care paramedics (ICP).

In November 2015, IM ketamine 4mg/kg was introduced for ICPs to administer to patients with severe agitation. This was expanded to ALS paramedics in March 2017.

Treatment protocol

When called to the scene for a patient with severe agitation, paramedics usually await arrival of police to assist in the safe restraint of the patient. Once the patient is safely restrained, ketamine is administered IM into the lateral thigh. When the patient has become sedated, oxygen by face mask is administered, a vital signs survey is undertaken and monitoring using pulse oximetry is commenced. In the event of recurrence of agitation during transport, repeat IM ketamine (by ALS paramedic) and/or IV midazolam (by ICP) may be administered. Rarely, IM ketamine may be administered to an adult without the presence of police, if multiple paramedics are present and the patient is able to be safely restrained. For children <16 years with severe agitation, consultation is undertaken with the receiving paediatric hospital.

Data collection

Data collection templates were securely sent to the 21 participating sites. Site investigators (SI) at the hospitals manually reviewed the patient records, provided the requested data and returned the file to Ambulance Victoria.

Data sources and definitions

Prehospital data were sourced from the Ambulance Victoria data warehouse. Hospital data were sourced from the patient record by a site investigator (SI) at 21 of the 32 hospital sites that patients were transported to across Victoria.

Severe agitation is defined as per the Ambulance Victoria clinical practice guidelines where there is a high risk of violence. The underlying cause of agitation and 'indication for sedation' represents the presumed aetiology at the time of ketamine administration, usually as described by bystanders. These assessments were categorised as a psychiatric episode (mental health related presentations including psychiatric episodes with no known alcohol or drug involvement) or substance induced episode (aggressive behaviour due to known or suspected drugs and/or alcohol intoxication).

The primary outcome measure was the time to adequate sedation which was defined as the time between administration of the first IM dose of ketamine and the time when physical restraint was no longer needed and the patient was able to receive oxygen administration and undergo vital sign survey.

An adverse event following sedation was defined according to previous studies, including hypoxia (oxygen saturation <90%), excessive salivation, requirement for intubation and emergence phenomena. An emergence phenomena was defined as the return of agitation, anxiety, distress or hallucination.

The Richmond Agitation Sedation Scale (RASS) was used to measure the patient agitation level and was estimated from the case notes recorded upon arrival at the hospital ED.[12]

Outcomes of interest

The primary outcome was the time to adequate sedation. Secondary outcomes included the rate of intubation, agitation level on hospital arrival, length of hospital stay, final ED disposition, final ED diagnosis and results of ED investigations including CT brain scan, drug and alcohol screening results (if performed).

Statistical analysis

Continuous variables are described using means (standard deviation [SD]) or medians (interquartile range [IQR]) and compared across groups using an independent samples t-test or Mann Whitney-U test as appropriate. Categorical data are presented as frequencies and proportions, with comparisons made using Pearson's chi-square or Fisher's exact test, as appropriate. A two-sided p-value of less than 0.05 was considered statistically significant for all analyses. All statistical analyses were performed using Stata Statistical Software: Version 15.1 (Stata Corporation, College Station, Texas, USA,)

Ethics

Ethics approval was granted by the Alfred Hospital Human Research Ethics Committee, Melbourne, Australia. Site specific ethics approval was granted from the 21 hospitals sites with data extracted from the medical record by the SI at that hospital.

Results

A total of 358 prehospital patients were administered IM ketamine by paramedics for severe agitation during the study period. Of the 358 prehospital patient records, 305 (85.2%) were matched to participating hospital ED records. Sample derivation is shown in Figure 1.

Patient and Baseline Characteristics

The baseline characteristics are presented in Table 1. The median age of patients was 31.0 years (IQR 23.0 – 40.0), most patients were male (71.2%) and had a documented mental health history (62.6%). There were 11 patients (3.1%) who were attended to by ambulance twice during the study period.

Two patients (0.6%) were attended to on four separate occasions within a three and four month period, respectively.

Prehospital results

More than half of the patients (64.0%) required sedation for a presumed substance induced episode. Of these, presumed illicit drugs were involved in the majority of substance abuse cases. The remainder (36%) had a presumed mental health episode.

The median initial ketamine dose was 3.8mg/kg (IQR 3.5-4.2). Adequate sedation was achieved in 96.9% of cases with the median time from ketamine administration to adequate sedation of 5.0 minutes (IQR 3.0-7.0; Range 1-31 minutes). Administration of IM midazolam prior to the administration of IM ketamine occurred in 84 (23.5%) patients however there was no significant difference in median time to effective sedation for patients given midazolam before ketamine (median: IQR: 4.0 (2.0, 7.0)) compared to patients given ketamine first (median: IQR: 5.0 (3.0, 7.0) (p=0.079)). The median on-scene time was 36.0 minutes (IQR 25.0, 51.3 mins). A total of 12 patients (3.4%) required a second dose of IM ketamine during transport.

Hospital results

The hospital investigations and management for the 305 matched hospital records are presented in Table 2. The median agitation score of patients on arrival at ED was -3.0 indicating 'moderate sedation' (IQR -4.0, 1.0) (Figure 2). The brain CT results were reported as 'normal' for the majority of patients who underwent this investigation (97.7%). Two patients had an abnormal brain CT with evidence of minor intracranial bleeding. Benzodiazepine (38.2%), cannabinoids (31.6%) and amphetamines (27.6%) were the most common drugs identified in the 76 (24.9%) patients that underwent urine drug screening. Over half of the patients (54.4%) were tested for a blood alcohol level with the majority of these (60.2%) recording a level below 0.05gm%. The median length of hospital stay was one day (IQR 1.0-3.0) and the majority of patients were discharged home from the ED (58.8%).

Adverse events

Adverse events observed during the prehospital phase of care were transient hypoxia in 18 (5.0%) patients, hyper-salivation in 15 (4.2%) and emergence reactions in three (0.8%) patients. After hospital arrival, adverse events were hypoxia in 13 (4.3%) cases. There were no documented cases of hyper-salivation or emergence reactions. A total of 45 (14.8%) patients were intubated, two in the prehospital environment and 43 after hospital arrival.

Of the two patients that underwent prehospital intubation, one patient was severely agitated secondary to apparent substance abuse but also sustained a closed head injury. The second patient was intubated due to persistent airway secretions and respiratory depression.

The rate of intubation after arrival at the ED for the hospitals that received more than 20 patients is shown in Table 3. There was marked variation in this intervention with physicians at one hospital intubating 52.2% of the 23 patients transported to that ED and physicians intubating none of the 26 patients transported to another ED.

Discussion

In this study, we describe the characteristics and outcomes of patients who received 4mg/kg of IM ketamine for severe agitation in the prehospital setting. We observed that ketamine was an effective drug for the rapid sedation of the severely agitated patients in the prehospital environment with a low rate of complications.

Our finding of a high rate of rapid, effective sedation is similar to previous studies on the use of prehospital IM ketamine in patients with severe agitation. In a recent meta-analysis of 13 studies of which 10 studies were conducted in the prehospital setting and three in the ED setting, the proportion of patients that achieved satisfactory sedation was 85%. [7]

The time between administration of a sedative and onset of effect is important. Given that these patients are usually being restrained by police, a prolonged time between drug administration and effective sedation may increase the risk of injury to both the patient and police. In a study that

evaluated a dose of 5mg/kg in 49 patients with severe agitation Cole *et al*. found that adequate sedation was achieved in 90% of cases in an average of 4.2 minutes.[6] In another observational study of 52 agitated patients, it was found that sedation with 4mg/kg ketamine achieved adequate sedation in two minutes, however that study did not report the method used to define this interval.[9]

Several previous studies have reported high rates of intubation after administration of IM ketamine. The overall proportion of subjects receiving airway intervention in the meta-analysis of 13 studies was 20%. [7] However, some studies have reported higher rates of intubation. In a study by Cole *et al*. study, 57% of patients were intubated following administration of prehospital IM ketamine.[6] In the Olives *et al.* study, 63% (85/135) were intubated.[10] Whilst our study had an overall intubation rate of 14.8%, there was a marked variation between hospitals in the rate of intubation after arrival at the ED. This variation in ED airway management in sedated/ overdose patients has previously been reported in a comparison of two Victorian EDs which also showed a marked difference in the intubation rates in patients presenting with overdose of the sedative drug GHB.[13] In that study, the intubation rate for unconscious GHB overdose patients at one hospital was 6% compared with 33% at the other hospital. In our study, the variation in the rate of intubation between these hospitals was higher (0.0% to 52.2%) and this was also associated with an increased requirement for admission to the ICU despite similar patient baseline characteristics. Reasons for the variation rate in intubation are unclear and would require further research. Possible factors may include variation in physician practice and/or variation in ED protocols for the management of unconscious patients.

Notwithstanding the supportive data from our experience, the optimal drug for use by paramedics to sedate severely agitated patients in the prehospital setting is uncertain. In a recent survey by Nambiar *et al.* of ambulance clinical practice guidelines in Australasia for initial IM sedation of patients with severe agitation, three ambulance services reported using ketamine, three reported using droperidol and four reported using midazolam, although several services allowed an alternate drug if the first did not provide for adequate sedation.[3]

The use of IM droperidol was compared with IM midazolam by Page *et al.* in a before/after study.[4] There were 141 agitated patients administered IM midazolam before a guideline change following which 149 patients were administered IM droperidol. The primary outcome of that study was the proportion of adverse effects. Fewer adverse events occurred with droperidol (11/149) compared to midazolam (33/141) (7% vs. 23%; absolute difference 16%; 95% confidence interval [CI]: 8% to 24%; p=0.0001). Median time to sedation was 22 min (interquartile range [IQR]:18 to 35 min) for droperidol compared to 30 min (IQR: 20 to 45 min) for midazolam.

There has been a randomised, controlled trial comparing 5mg/kg ketamine and 10mg/kg of IM haloperidol in patients with severe agitation in the prehospital setting.[10] In that study, ketamine was superior to haloperidol in time to adequate sedation (median time 5 min, range 0.4-23 mins compared with a median time 17 mins, range 2-84mins, respectively). However, complications in that study occurred in 49% (27/55) of patients receiving ketamine vs. 5% (4/82) in the haloperidol group. The rate of intubation was also significantly higher in the ketamine group with 39% of patients who received ketamine being intubated versus 4% of patients receiving haloperidol.

Limitations

This study is strengthened by the capture of prehospital electronic data immediately after each case is concluded. However, this study was retrospective in nature and carries the known limitations of this approach. Also, we were unable to follow up all patients who received IM ketamine since this would have required ethics approval at each site and a site investigator to manually retrieve data at that site. On the other hand, our study sites included a wide range of different hospitals in both metropolitan and rural areas and is therefore likely to accurately represent the overall hospital management of these patients.

Conclusion

We found 4mg/kg of IM ketamine to be effective with a short time to adequate sedation and low rate of prehospital complications. These findings suggest ketamine may be an effective pharmacological agent for managing patients with severe agitation in the prehospital setting. Reasons for the variation in ED intubation rates between hospitals are unclear and requires further research. Since droperidol is used in a number of Australian ambulance services, prospective trials comparing these two agents are required to determine the optimal sedation agent for this challenging patient group. Such studies should include ED and longer-term outcomes.

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Figure 1. Flow chart of study enrolment

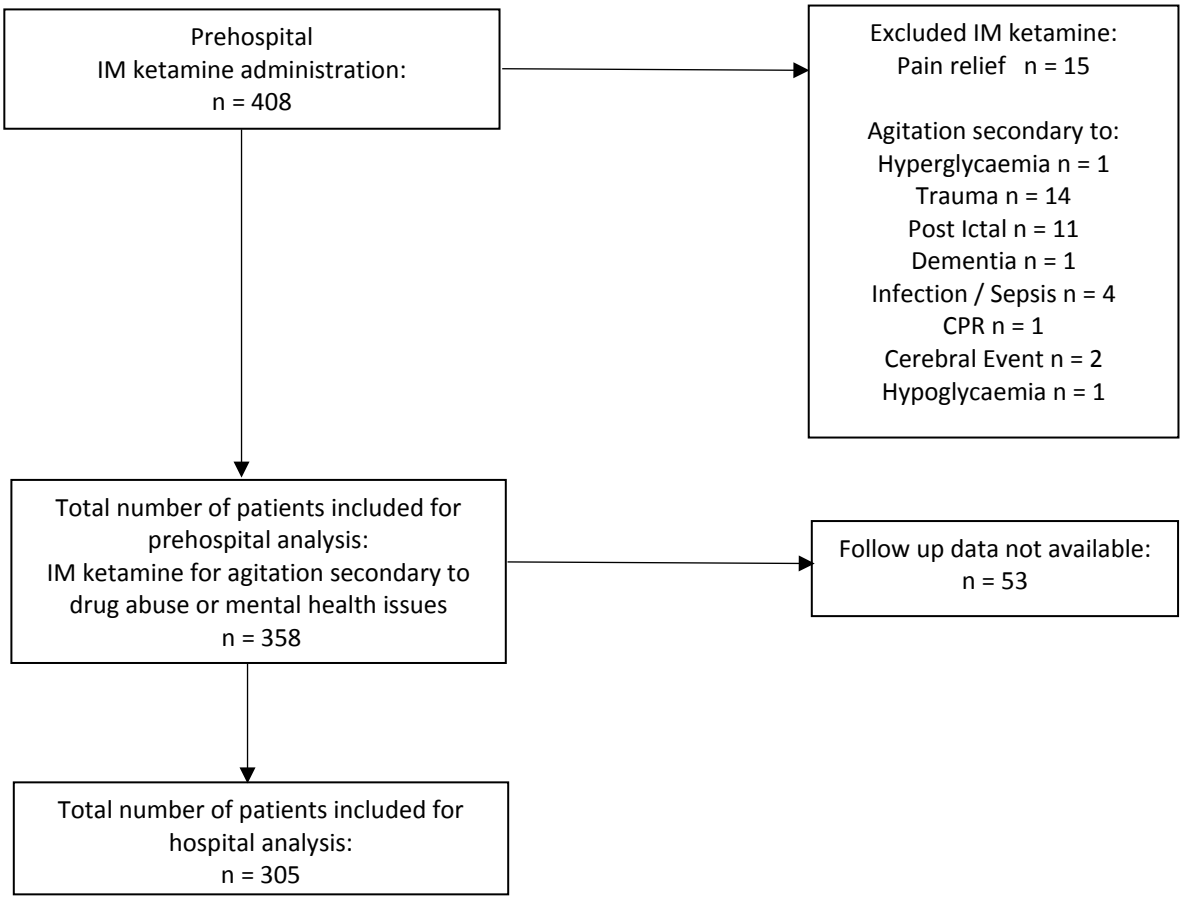

Table 1. Prehospital Characteristics and management

Characteristics and management	Overall (N =358)	
Age in years, median (IQR)	31.0 (23.0, 40.0)	
Age category, n (%)		
≤15 years	5 (1.4)	
16-39 years	256 (73.6)	
40-64 years	85 (24.4)	
≥ 65 years	2 (0.6)	
Male Sex, n (%)	255 (71.2)	
History of Mental Illness†, n (%)	n = 224	
Psychiatric History	152 (67.9)	
Substance Abuse	101 (45.1)	
Neurocognitive History	49 (21.9)	
Unknown History	101 (28.2)	
Police at scene	328 (91.6)	
Case times (min), median (IQR)		
Response time	18.0 (10.0, 32.0)	
Scene time	36.0 (25.0, 51.3)	
Transport time	15.0 (10.0, 27.0)	
Triage time	5.0 (2.0, 7.0)	
Off stretcher time	10.0 (6.0, 17.0)	
Hospital time	60.0 (45.5, 79.5)	
Total case time	138.0 (113.0, 166.0)	
Ketamine administration		
Indication for Sedation, n (%)		
Psychiatric Episode	129 (36.0)	
Substance induced episode	229 (64.0)	
Alcohol	31 (13.5)	
Drugs	162 (70.7)	
Both	36 (15.7)	
Initial Dose (mg/kg), median (IQR)	3.8 (3.5, 4.2)	
IM Midazolam administered first, n (%)	84.0 (23.5)	
Additional dose of IM ketamine administered, n (%)	12.0 (3.3)	
Time to effective sedation (min). median (IQR)	5.0 (3.0, 7.0)	
Adequate sedation	347.0 (96.9)	
Prehospital adverse events, n(%)		
Intubation	2.0 (0.6)	
Emergence reaction	3.0 (0.8)	
Transient hypoxia	18.0 (5.0)	
Hypersalivation	15.0 (4.2)	
Prehospital Vital Signs	**Before ketamine**	**After ketamine**
SBP (mmHg), mean (SD)	132.1 (19.6)	143.2 (24.1)
Pulse (beats/min), mean (SD)	108.7 (24.0)	112.3 (23.3)
Pulse Oximetry (%),median (IQR)	98.0 (96.0, 99.0)	98.0 (96.0, 99.0)

GCS, median (IQR)	14.0 (12.0, 15.0)	8.0 (3.0, 12.0)
Respiratory rate (breaths/min), median (IQR)	22.0 (18.0, 24.0)	18.0 (16.0, 22.0)

†Mental illness history categories are not mutually exclusive as such patients can appear in more than one category. Neurocognitive history includes seizures, autism, ADHD, down syndrome, intellectual impairment, acquired brain injury.

‡All proportions exclude missing data.

§SD, standard deviation; min, minutes; IQR, interquartile range.

Table 2. Hospital Investigations and Management

Investigations and Management	Overall Hospital (N =305)	
ED Admission Vital Signs		
SBP (mmHg), mean (SD)	130.4 (21.0)	
Pulse (beats/min), mean (SD)	97.8 (18.5)	
Temperature (degrees Celsius), median (IQR)	36.4 (36.0, 36.9)	
Pulse Oximetry (%),median (IQR)	98.0 (96.0, 100.0)	
Richmond Admission Agitation Score, median (IQR)	-3.0 (-4.0, 1.0)	
Adverse events in ED, n (%)		
Transient hypoxia (Oxygen sat<90%)	13.0 (4.3)	
ED Intubation†	45.0 (14.8)	
Airway protection	28.0 (62.2)	
Ongoing agitation or violence	10.0 (22.2)	
Expected return of agitation	3.0 (6.7)	
Respiratory failure	2.0 (4.4)	
General anaesthetic for surgery	2.0 (4.4)	
Hyper salivation	0.0 (0.0)	
ED Investigations, n (%)		
Chest X-ray	n=89	
Normal	77.0 (86.5)	
Aspiration	3.0 (3.4)	
Other change	9.0 (10.1)	
Brain CT	n=89	
Normal	87.0 (97.8)	
Abnormal	2.0 (2.2)	
Drug Screen‡	n=76	
Benzodiazepine	29.0 (38.2)	
Cannabinoids	24.0 (31.6)	
Amphetamine	21.0 (27.6)	
Paracetamol	15.0 (19.7)	
Methadone	4.0 (5.3)	
Lithium	1.0 (1.3)	
Other drug	2.0 (2.6)	
No drugs identified	14.0 (18.4)	
Blood Alcohol Level (g/dL)	n=166	
0-0.05	100.0 (60.2)	
0.06-0.15	18.0 (10.8)	
0.16-0.30	42.0 (25.3)	
0.31+	6.0 (3.6)	
Blood Gas Analysis[3]	Venous n =199	Arterial n=21
Serum Lactate (mmol/L), median (IQR)	2.4 (1.3, 3.7)	2.6 (1.6, 3.3)
pH, median (IQR)	7.3 (7.3, 7.4)	7.3 (7.3, 7.4)
pCO_2, median (IQR)	48.0 (43.0, 54.0)	48.0 (44.0, 51.0)
Serum bicarbonate (mmol/L), median (IQR)	24.0 (22.0, 26.0)	23.5 (21.4, 25.0)

Serum potassium (mmol/L), median (IQR)	3.9 (3.6, 4.2)	3.9 (3.7, 4.1)
Length of hospital stay	n = 266	
Days, median (IQR)	1.0 (1.0, 3.0)	
ED Disposition, n (%)		
Home	179.0 (58.8)	
Psych ward	54.0 (17.8)	
ICU	30.0 (9.9)	
Ward	21.0 (6.9)	
Other	20.0 (6.6)	
Final hospital diagnosis		
Drug / Alcohol OD	146.0 (47.9)	
Mental health	109.0 (35.7)	
Mental health & drug / alcohol OD	41.0 (13.4)	
Other	6.0 (2.0)	
Post-ictal	3.0 (1.0)	

†The intubation count includes the two patients intubated in the prehospital environment.

‡Drugs screened are not mutually exclusive and therefore include multiple responses. Drugs screened by hospitals varied with some hospitals only screening for paracetamol (5 patients) or specific drugs.

§Blood gas assumed to be venous when type was not specified.

¶All proportions exclude missing data.

Table 3. Characteristics of patients presenting at Hospitals that received > 20 patients

Characteristics	Hospital A	Hospital B	Hospital C	Hospital D	Hospital E	Hospital F	Hospital G‡	P-Value
Number of cases, n	23	23	25	23	27	27	26	
Age in years, median (IQR)	30.0 (22.0, 37.0)	33.0 (19.0, 47.0)	31.0 (27.0, 38.0)	29.5 (24.0, 34.0)	29.0 (22.0,38.0)	36.0 (28.0, 45.0)	34.5 (27.0, 37.5)	0.30
Male sex, n (%)	20 (87.0)	14 (60.9)	18 (72.0)	17 (73.9)	21 (77.8)	21 (77.8)	21 (80.8)	0.54
RASS, median (IQR)	-3.0 (-4.0,-3.0)	-2.0 (-2.0, 0.0)	-3.0 (-4.0, 2.0)	0.0 (-4.0 ,3.0)	-3.0 (-4.0,-1.0)	-3.0 (-4.0,1.0)	-	0.08
Indication for sedation, substance induced episode, n (%)	15 (65.2)	9 (39.1)	14 (56.0)	14 (60.9)	19 (70.4)	19 (70.4)	16 (61.5)	0.32
Intubation, n (%)	12 (52.2)	5 (21.7)	5 (20.0)	3 (13.0)	3 (11.1)	2 (7.4)	0 (0.0)	<0.001
ED Disposition ICU, n (%)	7 (30.4)	0 (0.0)	4 (16.0)	2 (8.7)	4 (14.8)	2 (7.4)	0 (0.0)	0.01

†All proportions exclude missing data.

‡Richmond Admission Agitation Scale (RASS) wasn't captured by Hospital G.

Figure 2: Hospital Admission Richmond Agitation Sedation Scale

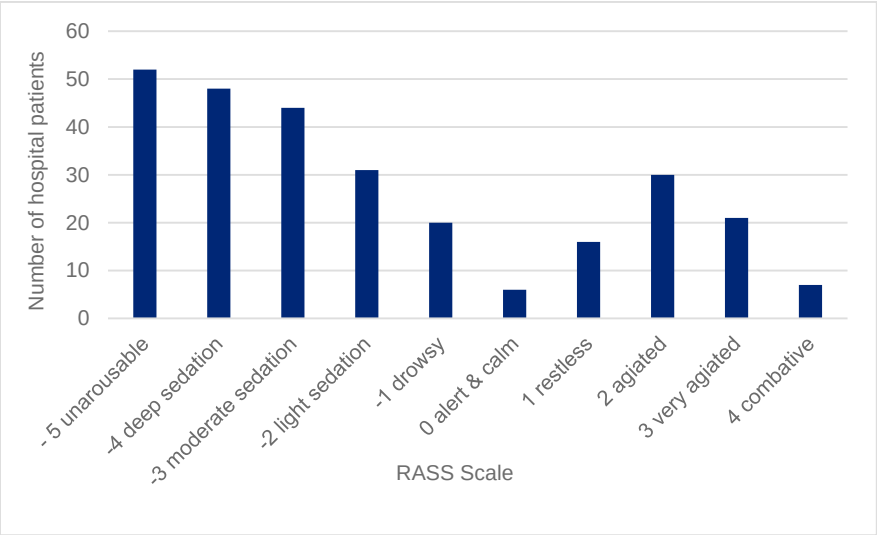

Figure 1. Flow chart of study enrolment

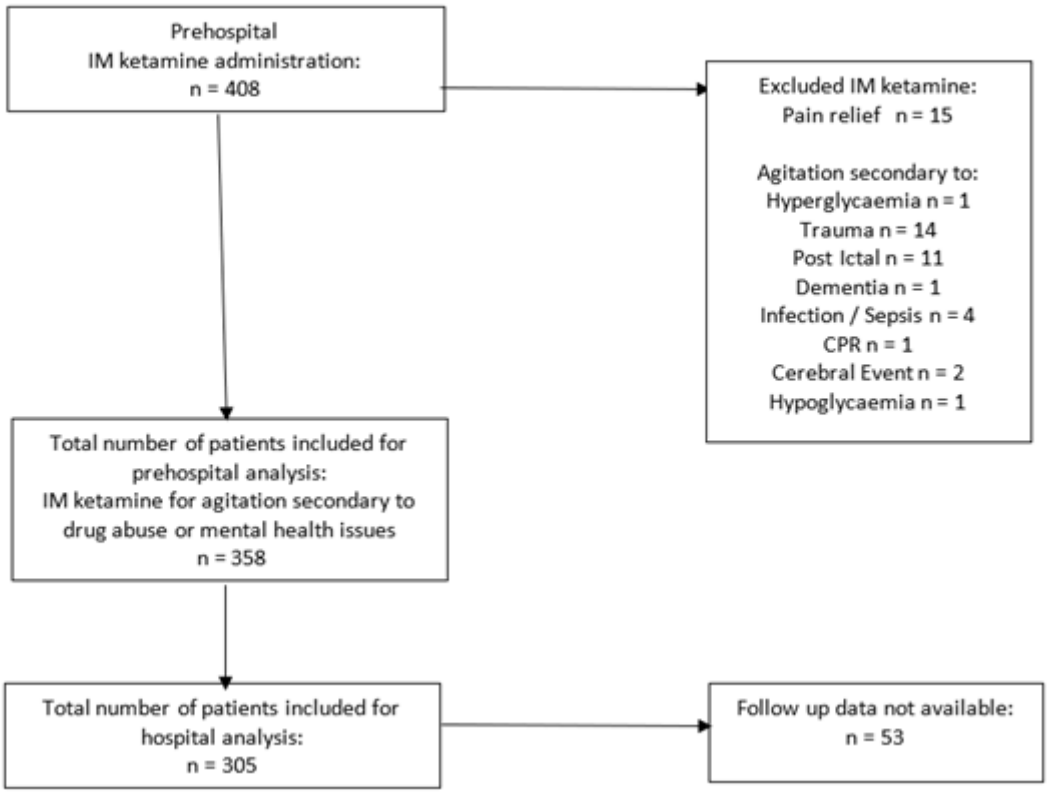

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Figure 2: Hospital Admission Richmond Agitation Sedation Scale

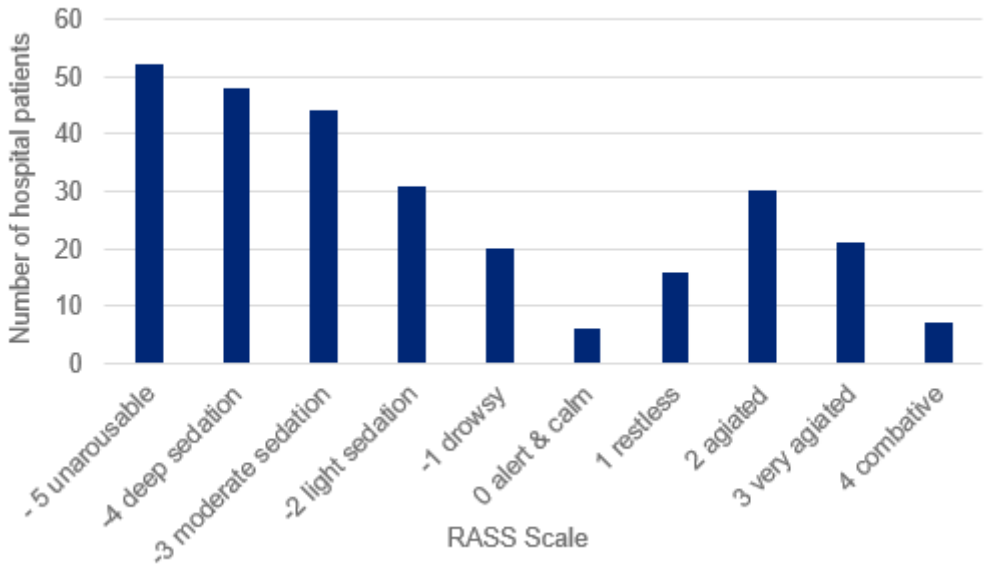

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Table 1. Prehospital characteristics and management

Characteristics and management	Overall (N =358)	
Age in years, median (IQR)	31.0 (23.0, 40.0)	
Age category, n (%)		
≤15 years	5 (1.4)	
16-39 years	256 (73.6)	
40-64 years	85 (24.4)	
≥ 65 years	2 (0.6)	
Male Sex, n (%)	255 (71.2)	
History of Mental Illness†, n (%)	n = 224	
Psychiatric History	152 (67.9)	
Substance Abuse	101 (45.1)	
Neurocognitive History	49 (21.9)	
Unknown History	101 (28.2)	
Police at scene	328 (91.6)	
Case times (min), median (IQR)		
Response time	18.0 (10.0, 32.0)	
Scene time	36.0 (25.0, 51.3)	
Transport time	15.0 (10.0, 27.0)	
Triage time	5.0 (2.0, 7.0)	
Off stretcher time	10.0 (6.0, 17.0)	
Hospital time	60.0 (45.5, 79.5)	
Total case time	138.0 (113.0, 166.0)	
Ketamine administration		
Indication for Sedation, n (%)		
Psychiatric Episode	129 (36.0)	
Substance induced episode	229 (64.0)	
Alcohol	31 (13.5)	
Drugs	162 (70.7)	
Both	36 (15.7)	
Initial Dose (mg/kg), median (IQR)	3.8 (3.5, 4.2)	
IM Midazolam administered first, n (%)	84.0 (23.5)	
Additional dose of IM ketamine administered, n (%)	12.0 (3.3)	
Time to effective sedation (min). median (IQR)	5.0 (3.0, 7.0)	
Adequate sedation	347.0 (96.9)	
Prehospital adverse events, n(%)		
Intubation	2.0 (0.6)	
Emergence reaction	3.0 (0.8)	
Transient hypoxia	18.0 (5.0)	
Hypersalivation	15.0 (4.2)	
Prehospital Vital Signs	**Before ketamine**	**After ketamine**
SBP (mmHg), mean (SD)	132.1 (19.6)	143.2 (24.1)
Pulse (beats/min), mean (SD)	108.7 (24.0)	112.3 (23.3)
Pulse Oximetry (%),median (IQR)	98.0 (96.0, 99.0)	98.0 (96.0, 99.0)
GCS, median (IQR)	14.0 (12.0, 15.0)	8.0 (3.0, 12.0)
Respiratory rate (breaths/min), median (IQR)	22.0 (18.0, 24.0)	18.0 (16.0, 22.0)

†Mental illness history categories are not mutually exclusive as such patients can appear in more than one category. Neurocognitive history includes seizures, autism, ADHD, down syndrome, intellectual impairment, acquired brain injury.

‡All proportions exclude missing data.

§SD, standard deviation; min, minutes; IQR, interquartile range.

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Table 2. Hospital Investigations and Management

Investigations and Management	Overall Hospital (N =305)	
ED Admission Vital Signs		
SBP (mmHg), mean (SD)	130.4 (21.0)	
Pulse (beats/min), mean (SD)	97.8 (18.5)	
Temperature (degrees Celsius), median (IQR)	36.4 (36.0, 36.9)	
Pulse Oximetry (%),median (IQR)	98.0 (96.0, 100.0)	
Richmond Admission Agitation Score, median (IQR)	-3.0 (-4.0, 1.0)	
Adverse events in ED, n (%)		
Transient hypoxia (Oxygen sat<90%)	13.0 (4.3)	
ED Intubation†	45.0 (14.8)	
Airway protection	28.0 (62.2)	
Ongoing agitation or violence	10.0 (22.2)	
Expected return of agitation	3.0 (6.7)	
Respiratory failure	2.0 (4.4)	
General anaesthetic for surgery	2.0 (4.4)	
Hyper salivation	0.0 (0.0)	
ED Investigations, n (%)		
Chest X-ray	n=89	
Normal	77.0 (86.5)	
Aspiration	3.0 (3.4)	
Other change	9.0 (10.1)	
Brain CT	n=89	
Normal	87.0 (97.8)	
Abnormal	2.0 (2.2)	
Drug Screen‡	n=76	
Benzodiazepine	29.0 (38.2)	
Cannabinoids	24.0 (31.6)	
Amphetamine	21.0 (27.6)	
Paracetamol	15.0 (19.7)	
Methadone	4.0 (5.3)	
Lithium	1.0 (1.3)	
Other drug	2.0 (2.6)	
No drugs identified	14.0 (18.4)	
Blood Alcohol Level (g/dL)	n=166	
0-0.05	100.0 (60.2)	
0.06-0.15	18.0 (10.8)	
0.16-0.30	42.0 (25.3)	
0.31+	6.0 (3.6)	
Blood Gas Analysis§	Venous n =199	Arterial n=21
Serum Lactate (mmol/L), median (IQR)	2.4 (1.3, 3.7)	2.6 (1.6, 3.3)
pH, median (IQR)	7.3 (7.3, 7.4)	7.3 (7.3, 7.4)
pCO_2, median (IQR)	48.0 (43.0, 54.0)	48.0 (44.0, 51.0)
Serum bicarbonate (mmol/L), median (IQR)	24.0 (22.0, 26.0)	23.5 (21.4, 25.0)
Serum potassium (mmol/L), median (IQR)	3.9 (3.6, 4.2)	3.9 (3.7, 4.1)
Length of hospital stay	n = 266	
Days, median (IQR)	1.0 (1.0, 3.0)	
ED Disposition, n (%)		
Home	179.0 (58.8)	
Psych ward	54.0 (17.8)	
ICU	30.0 (9.9)	
Ward	21.0 (6.9)	
Other	20.0 (6.6)	
Final hospital diagnosis		
Drug / Alcohol OD	146.0 (47.9)	
Mental health	109.0 (35.7)	
Mental health & drug / alcohol OD	41.0 (13.4)	
Other	6.0 (2.0)	
Post-ictal	3.0 (1.0)	

†The intubation count includes the two patients intubated in the prehospital environment.

‡Drugs screened are not mutually exclusive and therefore include multiple responses. Drugs screened by hospitals varied with some hospitals only screening for paracetamol (5 patients) or specific drugs.

§Blood gas assumed to be venous when type was not specified.

¶All proportions exclude missing data.

Table 3. Characteristics of patients presenting at Hospitals that received > 20 patients

Characteristics	Hospital A	Hospital B	Hospital C	Hospital D	Hospital E	Hospital F	Hospital G‡	P-Value
Number of cases, n	23	23	25	23	27	27	26	
Age in years, median (IQR)	30.0 (22.0, 37.0)	33.0 (19.0, 47.0)	31.0 (27.0, 38.0)	29.5 (24.0, 34.0)	29.0 (22.0,38.0)	36.0 (28.0, 45.0)	34.5 (27.0, 37.5)	0.30
Male sex, n (%)	20 (87.0)	14 (60.9)	18 (72.0)	17 (73.9)	21 (77.8)	21 (77.8)	21 (80.8)	0.54
RASS, median (IQR)	-3.0 (-4.0,-3.0)	-2.0 (-2.0, 0.0)	-3.0 (-4.0, 2.0)	0.0 (-4.0 ,3.0)	-3.0 (-4.0,-1.0)	-3.0 (-4.0,1.0)	-	0.08
Indication for sedation, substance induced episode, n (%)	15 (65.2)	9 (39.1)	14 (56.0)	14 (60.9)	19 (70.4)	19 (70.4)	16 (61.5)	0.32
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†All proportions exclude missing data.

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