Risk Factors for Sedation-Related Events During Acute Agitation Management in The Emergency Department

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Risk Factors for Sedation-Related Events During Acute Agitation Management in The Emergency Department

ABSTRACT

Objective

To describe the incidence, nature and risk factors for adverse events (AEs) among patients who received parenteral sedation for acute agitation in an emergency department (ED) setting.

Methods

We undertook a prospective observational study and a clinical trial of parenteral sedation for the management of acute agitation. We included agitated adult patients who required parenteral sedation from 2014 to 2017 in twelve Australian EDs, excluding those with incomplete information or aged under 18 years. The primary outcome was the number of patients who experienced at least one AE. Multivariable logistic regression was used to determine factors associated with AEs.

Results

904 patients were included in the analyses (62.3% male; median age 34 years; range 18 to 95 years). Of these, 144 (15.9%) patients experienced at least one AE. The most common AEs were oxygen desaturation (7.4%), airway obstruction (3.6%), bradycardia (1.9%), hypotension (1.7%), and prolonged QTc interval (1.3%). No deaths or serious AEs were reported. The following factors had an increased adjusted odds ratio (OR) for experiencing an AE: age 65 years and older (OR 2.8, 95% confidence interval [CI] 1.2 to 7.2), more than one type of parenteral sedation administered within 60 minutes (OR 2.1, 95% CI 1.4 to 3.1), and alcohol intoxication (OR 1.8, 95% CI 1.2 to 2.6).

Conclusions

Sedation-related AEs are common, especially respiratory events. Elderly patients, sedation with multiple sedatives within 60 minutes, and alcohol intoxication increased the risk.

INTRODUCTION

Patients with acute agitation are a common presentation to emergency departments (EDs). A recent study reported that approximately 3% of ED patients presented with acute agitation, and the majority of them required parenteral sedation.¹ Care for these patients comes with safety risks for both ED staff and the patients themselves.² As patients presenting with acute agitation can be highly complex with co-morbid medical and substance use issues, there is an increased risk of adverse events (AEs) following parenteral sedation.^{1,2} Nonetheless, few studies have investigated factors that potentially place these patients at greater risk for AEs.

Sedative medications such as benzodiazepines (e.g. midazolam), typical antipsychotics (e.g. haloperidol, droperidol), and atypical antipsychotics (e.g. olanzapine) are commonly prescribed to manage acute agitation in the ED setting. Previous clinical trials have assessed the efficacy and safety of parenteral sedation for the management of agitation in this ED setting.³⁻⁷ The need to administer additional study medications or any sedative medications within 60 minutes of the initial dose has been commonly reported.³⁻⁷ However, it is unknown whether the addition of different sedative medications increases the risk of AEs.

In addition, the incidence of AEs reported in these trials varies considerably, depending on the pre-specified definitions and the methods for monitoring and documentation. For example, in comparable patient populations, the AE rate for intramuscular droperidol has been reported to range from 6.0% to 40.0%.^{5, 7} As there is lack of uniformity in reporting AEs in these trials, it is difficult to compare the AE rates directly. Importantly, none of these efficacy focused trials have sufficient statistical power to identify factors associated specifically with AEs among the patients.

Whilst previous research has demonstrated that intoxication with illicit substances or alcohol are associated with the majority of acute agitation presentations,^{1-3, 5, 7} the impact of these ingested substances on the occurrence of sedation-related AEs remains understudied. There is limited evidence regarding other factors that may predispose a patient who has received parenteral sedation for acute agitation to AEs. Further investigation into which patient characteristics and treatment-specific variables are associated with the occurrence of AEs may improve patient safety and prevent serious complications in managing acute agitation in EDs.

This study aimed to describe the incidence and nature of AEs among patients who received parenteral sedation for acute agitation in the ED, and to identify risk factors associated with AEs in this patient population.

METHODS

Study Design and Setting

We analyzed data from a randomized controlled trial (RCT) of parenteral sedation for the management of acute agitation and a prospective observational study of patients in 12 Australian EDs.^{3, 8} The annual patient census of these EDs ranged from 50,000 to 100,000 patients. Each ED is supported by 24-hour co-located psychiatric services. Ethics approval for both studies were obtained from the individual governance offices and human research ethics committees.^{3, 8}

The RCT compared intravenous (IV) midazolam-droperidol combination, IV droperidol alone and IV olanzapine alone for the management of undifferentiated acute agitation in two EDs in Melbourne, Australia. Patients were enrolled between October 2014 and August 2015, inclusive.

These two EDs did not participate in the observational study to avoid overlapping between the samples. The observational study was undertaken in the EDs of ten other public, tertiary-referral hospitals across three Australian states (Victoria, Queensland, and New South Wales) between March 2015 and April 2017, inclusive. The observational study was designed to complement AE data obtained from the RCT, in order to increase the sample size for multivariable risk factor analysis.

Selection of Participants

Patients aged 18 years or older who required parenteral sedation for undifferentiated acute agitation in the participating EDs were enrolled. Cases enrolled more than once into the RCT or with incomplete information were excluded from the analyses. In the RCT, three patients were enrolled twice (about 3-4 hours apart) during the same presentation. Only the initial encounter was included in this analysis of the RCT and observational study patients to avoid double counting of the AE incidence and to improve the accuracy of the logistic regression model. Consecutive patient enrollment was undertaken by assigning patients to the next sequential study pack at their site for the RCT, however, convenience sampling was used for the observational study.

Methods of Measurements

It is the routine clinical practice in the participating EDs to have one-on-one nursing implemented post-sedation to monitor the patient's vital signs, airway patency and level of sedation. Adverse events were recorded immediately after the administration of parenteral sedation and throughout the ED length of stay. Adverse event data and the time of first parenteral sedation administration were prospectively collected by clinical staff using a designated case report form. To ensure data were collected in a consistent way across all sites by different nurses, definitions of both respiratory and hemodynamic AEs were stated on the case report form and all data were reassessed by the site investigators after the ED presentation, by reviewing the medical record and seeking clarification of any details from the clinicians who cared for the patient in the ED.

Both studies used the same definitions for the following AEs: respiratory AEs (i.e. hypoventilation [respiratory rate < 10 breaths/min], oxygen desaturation [oxygen saturation <90% mmHg], partial or complete airway obstruction); cardiovascular AEs (i.e. prolonged QTc [corrected QT > 500ms], tachycardia [heart rate > 100 beats per minute], bradycardia [heart rate < 60 beats per minute]); and other AEs (i.e. extrapyramidal side effects [EPSE], vomiting, anticholinergic side effects [e.g. urinary retention, dry mouth], falls and anaphylaxis). Clinical events such as oxygen desaturation, airway obstruction, hypotension and borderline prolonged QTc occurring during the sedation will only be able to be detected by nursing staff providing bedside routine care. If other AEs occurred following the sedation (e.g. EPSE), they would have been detected by the attending nursing staff or reported by the patient. Patients were only discharged home after any identified AEs were managed and after being medically cleared. Therefore, clinical events observed and documented by staff on the case report form are considered a reliable source of reported events detected in the ED. Causality of each AE was assessed by the site investigators using the World Health Organization definitions.⁹

Site investigators are ED physicians responsible for the conduct of the study at the participating sites. Most participating sites have two site investigators and they have contributed their time in-kind for this study. The role and responsibilities of site investigators including study promotion prior to the study commencement (e.g. conduct training sessions for both nurses and doctors in the ED about the inclusion criteria, AE documentation, etc.), data collection (i.e. collecting demographics data from medical records, assessing AEs reported on the case report form), site support (e.g. answering queries from local staff and the coordinating principal investigators), and assist in the preparation of progress reports and the manuscript. They were not blinded to the study aim.

Site investigators extracted data on patient demographics and treatment from medical records. Variables extracted retrospectively included gender, age, triage date and time, medication history (i.e. regular psychotropic medications and medications given by paramedics), first dose of parenteral sedation regimen, further parenteral sedation prescribed in the ED within 60 minutes of the first dose, need for mechanical restraint, illicit drugs and alcohol use immediately prior to presentation, final diagnosis and disposition.

149

150 **Data Analysis**

151 Sample size calculations were determined a priori for both the RCT³ and the observational
152 study.⁸ For the observational study, our initial sample size was calculated to be at least 1944
153 patients in order to be 95% certain that the AE rate would range between 11% and 14% (level of
154 significance 0.05). However, after recruiting 547 patients, the incidence of AE observed was
155 13.5% (74/547; [95% CI 10.9-16.7]), within the expected range. Whilst higher sample numbers
156 will lead to smaller confidence intervals and may increase the chance of detecting rare AEs, we
157 believe the current sample size which afforded 13.5% AEs appears to have captured the most
158 common types of AE related to the parenteral sedation in this setting.

159

160 Patient characteristics, treatment received, incidence and nature of AEs were analyzed
161 descriptively and are reported as frequencies and percentages. For AE data, we calculated
162 differences in proportions with associated 95% confidence intervals (CI) for patients who
163 received single or multiple types of parenteral sedation within 60 minutes, and for agitation with
164 or without alcohol intoxication.

165

166 Adjusted odds ratios (ORs) and 95% CIs were determined using multiple logistic regression. The
167 independent variables were selected according to clinical plausibility. All variables were entered
168 simultaneously into the model to determine the OR for any AE. As previous work has reported
169 high rates of respiratory AEs post sedation,^{1, 3, 6, 7} we created a second model using the same set
170 of independent variables to determine the OR for any respiratory AE (oxygen desaturation,
171 airway obstruction, or hypoventilation). The independent variables selected for both models
172 included age, gender, regular psychotropic medications, alcohol intoxication, drug intoxication,
173 need for mechanical restraint, sedatives were administered prior to parenteral sedation, and
174 whether multiple types of parenteral sedation were administered within 60 minutes. All variables
175 included in the model are categorical and the outcomes are dichotomous (i.e. yes vs no), hence
176 the assumptions related to extreme values, influential values, and assumption of linearity are not
177 applicable for this model. Collinearity diagnostics were conducted, all variables have tolerance
178 values more than 0.1, which indicated low intercorrelations among the independent variables
179 included in the logistic regression model. Model fit was assessed for each model with the

Hosmer-Lemeshow fit statistic. All analyses were performed using IBM SPSS Statistics Version 25 (Armonk, NY: IBM Corp.) and the level of significance was 0.05.

RESULTS

Characteristics of study subjects

Of the 925 cases (361 from the RCT and 564 from the observational study) entered into the study database, 21 cases were excluded (one aged less than 18 years, three repeated enrolment, and seventeen incomplete information). The remaining 904 cases (357 from the RCT and 547 from the observational study) had complete data and were included in these analyses.

Patient characteristics, type of parenteral sedation administered, and disposition are reported in **Table 1**. The median age was 34 years (range 18 to 95). Among the 388 (42.9%) patients identified to have ingested alcohol prior to the ED presentation, approximately one half (46%) had blood alcohol levels documented. The mean (SD) alcohol level among these patients was 0.21 (0.10) g/dL.

Main Results

Adverse events following parenteral sedation were observed in 144 (15.9%) patients (**Table 2**). Respiratory AEs including oxygen desaturation, airway obstruction and hypoventilation were observed in 11.3% of patients. All patients who experienced a respiratory AE were managed with the administration of oxygen, airway positioning, or bag-mask ventilation. No patient required endotracheal intubation. Cardiovascular AEs including hypotension, QTc prolongation and bradycardia were observed in 4.8% of patients. However, significantly more patients receiving only olanzapine experienced at least one cardiovascular AEs (8.5% vs 4.2%, $p=0.04$). Bradycardia was the most commonly reported cardiovascular AE (17/43, 40%), and more than one-third (35%) of these patients were managed with olanzapine alone. All reported AEs were transient and resolved without adverse clinical outcomes. No deaths were reported.

We found no significant differences in ED length of stay and disposition destination between patients who experienced an AE and those who did not (**Table 1**). Although a higher proportion

of patients who experienced an AE were admitted to the medical ward, all patients were admitted for their underlying medical conditions. No patients were admitted to the medical ward secondary to AEs associated with the management of their acute agitation.

After adjustment for other variables, multiple types of parenteral sedation administered within 60 minutes (OR 2.1, 95% CI 1.4 to 3.1) and alcohol intoxication (OR 1.8, 95% CI 1.2 to 2.6) were independently associated with the occurrence of any AEs and with any respiratory AEs (**Table 3**).

DISCUSSION

To our knowledge, this study is the first to investigate the risk of the occurrence of any AEs in patients who received multiple types of parenteral sedation within 60 minutes of the initial parenteral sedation. To date, most studies related to the management of acute agitation have focused on the efficacy and safety of the initial dose of sedative medication.^{10, 11} As most of the sedative medications used in the ED setting for acute agitation have elimination half-lives longer than 60 minutes, any additional sedative medications administered within 60 minutes would likely have additive sedative and respiratory or hemodynamic depression effects.¹⁰ Hence, in comparison to patients who received only one type of parenteral sedation, agitated patients who received more than one type of parenteral sedation within 60 minutes are at higher risk of experiencing sedation-related AEs. When a different type of parenteral sedation is required to manage an episode of agitation, experienced staff and resuscitation equipment should be immediately available for prompt management of any sedation-related AEs.

Adverse events following parenteral sedation for acute agitation are common. Consistent with previous studies,⁴⁻⁷ respiratory-related AEs were the most common complications following parenteral sedation in this study. Although previous reviews highlight the potential for serious sedation-related AEs (e.g. Torsades de Pointes [TdP], respiratory depression),^{11, 12} it is important to note that, in this study, no patient experienced more than transient morbidity associated with sedation. Regular clinical monitoring with early detection of AEs, may have avoided life-

threatening events such as respiratory arrest. This finding serves to emphasize that all patients must receive close monitoring of their vital signs and be attended by personnel skilled in airway management when parenteral sedation is administered.

Droperidol is widely used in the management of acute agitation due to its effectiveness in treating all subsets of acute agitation, including those resulting from stimulant abuse,^{13, 14} alcohol intoxication,¹⁵ head injury,¹⁶ mania or psychosis^{17, 18} and in both elderly¹⁹ and paediatric²⁰ patients. However, the use of droperidol decreased considerably in the United States of America (USA) after the Food and Drug Administration placed a “black box” warning on its use in 2001.^{21, 22} This warning highlighted the potential risk of QT prolongation, TdP and sudden death in patients receiving droperidol at the recommended doses. However, our findings indicate that patients receiving droperidol alone reported the lowest incidence of sedation-related AEs. The finding that no patient developed TdP, is consistent with previous reports that the absolute risk of TdP is low.^{10,12-16,19,26} Our findings, therefore, provide additional data to support the safety profile of droperidol for sedation of agitated patients in the ED.

Considering the droperidol shortage in the USA following the black box warning and similar effects and comparable safety profile of droperidol and olanzapine,^{6, 14} olanzapine has been the first choice of initial parenteral sedation for acute agitation in some EDs.^{23, 24} While previous studies examining patients receiving olanzapine in the ED have reported a low rate of cardiovascular AEs,^{6, 23, 25, 26} we found that when compared with patients receiving other parenteral sedation regimens, cardiovascular AEs were more commonly experienced by patients receiving only olanzapine. Bradycardia occurred more frequently than hypotension and QTc prolongation. However, all cardiovascular AEs resolved without sequelae. Despite the difference, our findings add to the published literature supporting the safe use of parenteral olanzapine in ED patients.

Alcohol intoxication is a known risk factor for sedation-related AEs.^{27, 28} Consistent with previous studies, reduction in oxygen saturation was the main respiratory complication in this

subgroup of patients.^{24, 29} One previous study identified that parenteral sedation was associated with increased odds for use of critical care resources by patients with alcohol intoxication and acute agitation presenting to the ED.³⁰ Given alcohol has additive effects with other central nervous system depressant medications, regardless of the type of parenteral sedation administered, a high level of vigilance should be maintained following administration of parenteral sedation to patients with alcohol intoxication.

Although being elderly, especially aged 65 years and above, is associated with increased odds of experiencing a sedation-related AE when compared with those aged 30 years or less, the proportion of patients sedated for acute agitation in this older age group was relatively small. In this study, it is difficult to distinguish whether the increased risk of harm is due to underlying medical co-morbidities, or other unidentified factors not present in younger patients. Future research with a larger sample size is required to provide a more precise evaluation of this relationship.

LIMITATIONS

This study has several limitations. It was an analysis of data from a RCT and an observational study, which may introduce selection bias. However, as both studies involved adult patients with severe acute agitation that required parenteral sedation, the risk of selection bias is likely to be low. Furthermore, because the occurrence of AEs was monitored and documented in a similar method for both studies, the differences in the study design are unlikely to change the findings.

Theoretically, the risk of sedation-related events can be dose-dependent or medication-specific. However, statistical comparisons of AEs associated with different dosage regimens for each sedative medication were not performed, as the statistical power was low when comparing across subgroups. Similarly, we were unable to examine the association between AEs and route of sedative administration (i.e. intravascular vs intramuscular) as some patients received both intravascular and intramuscular sedation within 60 minutes of the initial parenteral sedation.

This study is also limited by the small numbers of intoxicated patients with a documented blood alcohol level. Final diagnosis of alcohol and illicit drug intoxication was decided by the treating clinician based on historical information, clinical presentation, and/or blood alcohol level. Specific diagnosis tests were only done where required as part of routine clinical care, therefore the prevalence of alcohol and illicit drug intoxication may be an underestimate. Although alcohol intake appears to be associated with decreasing oxygen saturations, our study was not powered to determine the association between blood alcohol level and the occurrence of AEs. It is also possible that lack of documentation may have led to non-identification of some intoxicated patients. Hence, we may have underestimated the true risk of alcohol intoxication.

Pre-treatment electrocardiograms (ECGs) are not routinely obtained in the ED for patients with severe agitation, so it is not known whether the QTc prolongations were pre-existing conditions or medication-induced. The low incidence of QTc prolongation in this analysis, and the finding that no patient developed TdP, is consistent with previous reports that the absolute risk of TdP related to parenteral sedation in this group of patients is small.^{6, 31} However, firm conclusions cannot be made because the study was not powered to compare QTc intervals, and not all patients had an ECG performed.

CONCLUSIONS

In summary, patients presenting with acute agitation, especially those aged 65 years and older, intoxicated with alcohol or managed with multiple types of parenteral sedation, carry increased risk of sedation-related AEs. Decades of research has shown that antipsychotics and benzodiazepines, alone or in combination, are effective for use in the management of acute agitation. Although all medications currently used for sedation carry a risk of AEs, our findings suggest that the majority of the AEs can be managed with relatively minor interventions. Hence, an emphasis should be placed on close physiologic monitoring to ensure early detection and management of these AEs, regardless of the type of parenteral sedation administered to manage the acute agitation.

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Table 1. Characteristics of the study population.

Characteristics	Total Population (N=904)	Any AE (n=144)	Respiratory AE (n=92)
Age, years, n (%)			
18-30	321	47 (14.6)	32 (10.0)
31-64	549	89 (16.2)	57 (10.4)
≥ 65	34	8 (23.5)	3 (8.8)
Male, n (%)	563	100 (17.8)	69 (12.3)
ICD-10 category, n (%)			
Mental illness	347	49 (14.1)	26 (7.5)
Intoxication (drugs and/or alcohol)	472	80 (17.0)	56 (11.9)

Risk factors for sedation-related events during acute agitation

Characteristics	Total Population (N=904)	Any AE (n=144)	Respiratory AE (n=92)
Organic illness	85	15 (17.6)	10 (11.8)
Regular psychotropic medications, n (%) ^a			
Benzodiazepines	91	13 (14.3)	6 (6.6)
SSRI or SNRI	84	17 (20.2)	10 (11.9)
Atypical antipsychotics	153	22 (14.4)	13 (8.5)
Typical antipsychotics	33	2 (6.1)	1 (3.0)
Prescription opioids ^b	70	5 (7.1)	2 (2.9)
Alcohol intoxication, n (%)	388	77 (19.9)	55 (14.2)
Illicit drug intoxication, n (%)	391	61 (15.6)	37 (9.5)
Need for mechanical restraint	494	89 (18.0)	63 (12.8)
Sedatives administered prior the initial parenteral sedation, n (%)			
Intramuscular midazolam ^c	32	9 (25.7)	6 (18.8)
Oral diazepam	43	7 (16.3)	5 (11.6)
Oral olanzapine	25	2 (8.0)	1 (4.0)
Oral risperidone	4	2 (50.0)	0 (0.0)
Oral diazepam and olanzapine	26	4 (15.4)	3 (11.5)
Type of parenteral sedation administered within 60 minutes, n (%)			
Single sedative			
Droperidol	473	54 (11.4)	32 (6.8)
Olanzapine	118	22 (18.6)	10 (8.5)
Midazolam	48	6 (12.5)	5 (10.4)
Others ^d	10	2 (20.0)	1 (10.0)
Multiple sedatives			
Midazolam + antipsychotics ^e	217	54 (24.9)	41 (18.9)
Typical antipsychotics + atypical antipsychotics ^f	19	3 (15.8)	0 (0.0)
Ketamine + other sedatives ^g	10	3 (30.0)	3 (30.0)
Other combinations ^h	9	0 (0.0)	0 (0.0)
ED length of stay, hours, median (IQR)	10.1	9.2	8.9

Risk factors for sedation-related events during acute agitation

Characteristics	Total Population (N=904)	Any AE (n=144)	Respiratory AE (n=92)
	(6.0 to 15.2)	(5.4 to 14.3)	(5.6 to 12.3)
Disposition, n (%)			
Home	474	71 (15.0)	52 (11.0)
Psychiatric ward	282	40 (14.2)	22 (7.8)
Medical ward	79	17 (21.5)	8 (10.1)
ED observational ward	44	12 (27.3)	7 (15.9)
Other facilities ⁱ	25	4 (16.0)	3 (12.0)

ICD-10=International Classification of Diseases; IQR= Interquartile range SSRI=selective serotonin reuptake inhibitor; SNRI=serotonin noradrenalin-reuptake inhibitor

^a Patients could have been administered more than one type of regular psychotropic medications prior to the presentation.

^b Prescription opioids included buprenorphine, codeine, fentanyl, methadone, morphine, oxycodone, tramadol

^c Intramuscular midazolam administered by paramedics before arriving emergency departments.

^d Other sedative medications included haloperidol, diazepam, lorazepam, and propofol.

^e Antipsychotics that had been administered within an hour before or after sedation with midazolam included droperidol, olanzapine, and haloperidol.

^f Combination of antipsychotics included droperidol-olanzapine, and haloperidol-risperidone.

^g Sedatives that had been administered within an hour before or after sedation with ketamine included midazolam, droperidol, clonazepam, and morphine.

^h Other combinations of sedatives included droperidol-diazepam, droperidol-clonazepam, and droperidol-lorazepam.

ⁱ Other facilities included correctional facilities, assisted accommodation and police

Risk factors for sedation-related events during acute agitation

Table 2. Frequency and nature of sedation-related adverse events.

	Total N=904	Multiple sedatives n=255	Single sedative n=649	Difference in proportions (95% CI)	Alcohol n=388	No Alcohol n=516	Difference in proportions (95% CI)
Number of patients with reported events, n (%)	144 (15.9)	60 (23.5)	84 (12.9)	10.6 (4.8 to 16.9)	77 (19.8)	67 (13.0)	6.9 (1.9 to 12.0)
Respiratory, n (%)							
Oxygen desaturation (SaO ₂ <90%)	67 (7.4)	32 (12.6)	35 (5.4)	7.2 (2.9 to 12.3)	42 (10.8)	25 (4.8)	6.0 (2.3 to 10.0)
Airway obstruction (partial or complete)	33 (3.6)	17 (6.7)	16 (2.5)	4.2 (1.1 to 8.3)	20 (5.2)	13 (2.5)	2.7 (-0.02 to 5.7)
Hypoventilation (RR <10 breaths/min)	6 (0.7)	1 (0.4)	5 (0.8)	-0.4 (-1.8 to 1.6)	3 (0.8)	3 (0.6)	0.2 (-1.2 to 1.9)
Cardiovascular, n (%)							
Bradycardia (HR <60 beats/min)	17 (1.9)	1 (0.4)	16 (2.5)	-2.1 (-0.3 to 3.7)	7 (1.8)	10 (1.9)	-0.1 (-2.1 to 2.1)
Hypotension (SBP <80 mmHg)	15 (1.7)	7 (2.8)	8 (1.2)	1.6 (-0.5 to 4.7)	10 (2.6)	5 (1.0)	1.6 (-0.3 to 3.9)
Prolonged QTc (QTc interval >500ms)	12 (1.3)	4 (1.6)	8 (1.2)	0.4 (-1.3 to 3.1)	7 (1.8)	5 (1.0)	0.8 (-0.9 to 3.0)
Tachycardia (HR >100 beats/min)	1 (0.1)	0 (0.0)	1 (0.2)	-0.2 (-1.7 to 1.0)	0 (0.0)	1 (0.2)	-0.2 (-1.0 to 1.3)
Others, n (%)							
EPSE	8 (0.9)	5 (2.0)	3 (0.5)	1.5 (-0.09 to 4.3)	1 (0.3)	7 (1.4)	-1.1 (-0.5 to 2.7)

Risk factors for sedation-related events during acute agitation

	Total N=904	Multiple sedatives n=255	Single sedative n=649	Difference in proportions (95% CI)	Alcohol n=388	No Alcohol n=516	Difference in proportions (95% CI)
Vomiting	2 (0.2)	1 (0.4)	1 (0.2)	0.2 (-0.7 to 2.4)	1 (0.3)	1 (0.2)	0.1 (-0.1 to 1.5)
Urinary retention	2 (0.2)	1 (0.4)	1 (0.2)	0.2 (-0.7 to 2.4)	0 (0.0)	2 (0.4)	-0.4 (-0.9 to 1.5)
Dry mouth	1 (0.1)	0 (0.0)	1 (0.2)	-0.2 (-1.7 to 1.0)	0 (0.0)	1 (0.2)	-0.2 (-1.0 to 1.3)
Fall	1 (0.1)	1 (0.4)	0 (0.0)	0.4 (-0.4 to 2.5)	1 (0.3)	0 (0.0)	0.3 (-0.7 to 1.7)
Anaphylaxis	1 (0.1)	0 (0.0)	1 (0.2)	-0.2 (-1.7 to 1.0)	0 (0.0)	1 (0.2)	-0.2 (-1.0 to 1.3)
Total cases of AEs, n (%)	166 (18.3)	70 (27.5)	96 (14.8)	12.7 (6.6 to 19.2)	92 (23.7)	74 (14.3)	9.4 (4.1 to 14.8)

AE=adverse event; EPSE= Extrapyramidal side effects; HR= heart rate; QTc= corrected QT interval; RR= respiratory rate; SaO₂= oxygen saturation;

SBP=systolic blood pressure

Table 3. Multivariable logistic regression model for adverse events for total population (n=904).

Variables	Any AE		Respiratory AE	
	OR*	(95% CI)	OR*	(95% CI)
Age, years				
18-30 ^a	-	-	-	-
31-64	1.2	(0.8 to 1.8)	1.1	(0.7 to 1.8)
≥ 65	2.8	(1.1 to 7.1)	1.5	(0.4 to 5.7)
Male	1.4	(1.0 to 2.1)	2.0	(1.2 to 3.3)
Regular psychotropic medications	0.9	(0.6 to 1.3)	0.8	(0.5 to 1.3)
Alcohol intoxicated	1.8	(1.2 to 2.6)	2.2	(1.4 to 3.5)
Illicit drug intoxicated	1.0	(0.7 to 1.5)	0.8	(0.5 to 1.3)
Need for mechanical restraint	1.3	(0.9 to 1.9)	1.6	(1.0 to 2.6)
Sedatives were administered prior parenteral sedation	1.3	(0.8 to 2.1)	1.3	(0.7 to 2.4)
Multiple types of parenteral sedation were administered within 60 minutes	2.1	(1.5 to 3.1)	2.6	(1.6 to 4.1)

*Adjusted odds ratio (OR) generated by the simultaneous entry of covariates in the logistic regression model. The P value for Hosmer-Lemeshow goodness-of-fit statistics for all AE and respiratory AE is 0.990 and 0.815, respectively.

^a Reference group with which other groups are compared.

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