Signa Vitae

ORIGINAL RESEARCH

Prehospital drugs for sedation in psychomotor agitation, friends or foes? An observational retrospective study

Serena Tomasino[1], Giulio Trillo'[2], Annarita Tullio[3], Elena Querena[4],
Emiliano Fattori[1,5], Chiara Molinari[1,5], Francesco Meroi[1,5,]*, Tiziana Bove[1,5]

[1] Department of Anesthesia and Intensive Care Medicine, ASUFC University-Hospital of Central Friuli, 33100 Udine, Italy

[2] E.M.S.-SUEM-118, AULSS 1 Dolomiti, Pieve di Cadore Hospital, 32044 Pieve di Cadore, Italy

[3] Epidemiology and Public Health Unit, ASUFC University-Hospital of Central Friuli, 33100 Udine, Italy

[4] Department of Anesthesia and Intensive Care Medicine, A.O.U.I. University Hospital of Verona, 37126 Verona, Italy

[5] Department of Medicine (DAME), University of Udine, 33100 Udine, Italy

*Correspondence
francesco.meroi@asufc.sanita.fvg.it
(Francesco MEROI)

Abstract

Altered mental status (AMS) describes an undifferentiated presentation of disorders of mentation. It represents a common problem for prehospital and hospital providers and may be found in 5% to 10% of patients admitted to the Emergency Department (ED). Psychomotor Agitation (PMA), a state of motor restlessness and mental tension associated with a variety of psychiatric conditions, is one of the most frequent manifestations of AMS. In this observational retrospective study we included all the patients who presented PMA, treated by the out-of-hospital Emergency Medical System (EMS), and transported to the ED of the University Hospital of Udine, Italy. The objectives were to determine the incidence of patients with PMA treated by EMS in the area of investigation, the evaluation of pharmacologically treated patients considering the most commonly administered drugs, the intubation rate, the fraction of inspired oxygen (FiO_2) needs, the length of hospital stay (LOHS), the adverse drug reactions (ADRs), and the excited delirium syndrome (ExDS). From January 2017 to December 2018, 319 patients were enrolled. The prevalence of PMA was 2.5% and 0.5% were the cases of PMA managed by the EMS. The predominant drugs used for sedation were midazolam (19.75%) and ketamine (9.09%), alone or in association; patients with consistent PMA required more than one sedative. Statistically significant differences were found in FiO_2 supplementation for ketamine-sedated psychiatric patients and midazolam-sedated psychiatric patients with chronic home therapy, in the LOHS >24 hours (h), with a longer stay in case of midazolam and ketamine use, and in LOHS and FiO_2 supplementation due to polypharmacy administration with more than one sedative drug. PMA is a frequent and widespread phenomenon and in the prehospital setting requires rapid assessment and management. Therapeutical strategies with benzodiazepines, ketamine, and rarely associations of drugs are safe, do not increase hypoxia and intubation rate.

Keywords

Psychomotor agitation; Ketamine; Midazolam; Emergency medical system; Prehospital care

1. Background

Altered mental status (AMS) describes the undifferentiated presentation of disorders of mentation, including impaired cognition, diminished attention, reduced awareness, and altered level of consciousness. AMS may be found in 5% to 10% of patients in Emergency Departments (ED) [1]. In a retrospective study, Kanich and colleagues found that the most common discharge diagnoses accounting for AMS were neurologic (28%) and toxicologic (21%), followed by trauma (14%), psychiatric (14%), infectious (10%), endocrine/metabolic (5%), pulmonary (3%), oncologic (3%), cardiovascular (1%), gastrointestinal (1%), and renal (1%) [2].

In particular, psychomotor agitation (PMA) is a state of motor restlessness and mental tension associated with a variety of psychiatric conditions including schizophrenia, major depression, bipolar personality, general anxiety, and panic disorders, as well as drugs or alcohol abuse or withdrawal [3]. It is a common problem for prehospital providers and accounts for 2.6% of the admissions to the ED [4]. Emergent PMA requires appropriate assessment and management in order to minimize the anxiety of the patient and reduce the risk for escalation and violence [5, 6]. Profound agitation may culminate in excited delirium syndrome (ExDS), a syndrome with uncertain, likely multiple, etiologies, characterized by delirium, agitation, acidosis, and hyperadrenergic autonomic

dysfunction, typically in the setting of acute-on-chronic drug abuse or serious mental illness [7].

This study aims to quantify the incidence of PMA in the area of our investigation and to identify which techniques and therapies are the most effective for its management, considering that the optimal drug for rapid, complete, and reversible sedation of agitated patients in the prehospital environment is not known.

2. Methods

2.1 Study design and setting

This study was designed as a single-center observational retrospective study and was conducted at the University Hospital of Udine, Italy. The out-of-hospital Emergency Medical System (EMS) serves an urban and suburban population of over 207,000 (2018), covering 236.73 km^2.

2.2 Selection of participants

All medical reports of patients with agitation and aggressive behavior treated by our out-of-hospital EMS were retrospectively screened. Inclusion criteria were: patients aged 18 years or more, who had a diagnosis of PMA for a psychiatric disease or alcohol or drugs abuse and required verbal de-escalation or pharmacological sedation. Exclusion criteria were: all cases of PMA associated with a functional, neurologic, metabolic, endocrinologic, infectious, and traumatic etiology.

2.3 Data collection

We searched in our emergency management software all cases of PMA in the study period, according to the inclusion and exclusion criteria. Demographic and clinical characteristics such as age and gender, medical history and home pharmacological therapies. We reported drugs administrated by the out-of-hospital EMS physicians (specialized in intensive care or emergency medicine), their routes of administration, and ADRs. For each patient were recorded events such as hypoxia, need for oxygen supply, FiO$_2$, need for intubation, vital parameters, metabolic acidosis, hyperthermia, arrhythmias, and ExDS.

2.4 Statistical analysis

The study population features have been investigated by performing descriptive statistics on categorical and continuous variables. Frequency distributions were used for categorical variables. For continuous variables, we considered mean, median, interquartile range, standard deviation, 25°, and 75° percentile, and minimum and maximum values. Kolmogorov-Smirnov test was performed to validate the normality of the distribution for continuous variables.

Since the continuous variables were not normally distributed, a non-parametric test such as Wilcoxon rank sum test was used. Chi-square test and Fisher's exact test were used for comparing qualitative data between two groups. Multiple logistic regressions with odds ratio (OR) (95% confidence interval (CI)) calculation have been performed. All statistical analyses were performed using R software version 4.0.2 (R Core Team (2020), Wien, Austria). The significance level was set at 0.05.

2.5 Outcome measures

The primary outcome of this study was to determine the incidence of patients with PMA treated by EMS in the area of investigation comparing it to the literature data. The secondary outcomes were the evaluation of pharmacologically treated patients considering the most commonly administered drugs, the evaluation of intubation rate in sedated patients, fraction of inspired oxygen (FiO$_2$) needs, the length of hospital stay (LOHS), adverse drug reactions (ADRs) and ExDS among the study population. Complications such as respiratory depression, desaturation, hemodynamic instability, arrythmias, allergic reactions, hypersalivation, apnea, aspiration/vomiting, laryngospasm, and seizures were analyzed.

3. Results

From 01 January 2017 to 31 December 2018, a total of 122,667 patients were admitted to the ED of the University Hospital of Udine, and 3076 (2.5%) received a diagnosis of PMA by the EMS medical doctor. In the cohort of patients admitted to ED exclusively from out-of-hospital emergency ground service, the prevalence of PMA was 0.5%. 133 females and 129 males were included in the study, with a mean age of 50.7 years (standard deviation (SD) ± 20.65); for 57 patients the gender was not registered. (Fig. 1) The main characteristics of the enrolled population are shown in detail in Table 1.

Verbal de-escalation was performed in 23 subjects (7.21%) and a mandatory medical treatment was necessary for 11 patients (4.09%). To reach an appropriate level of sedation, midazolam was the most frequent medication used in 63 patients (19.75%), followed by ketamine in 29 (9.09%), and diazepam in 21 patients (6.58%). Less frequently were administrated sodium thiopental (1.57%), fentanyl (0.31%) and haloperidol (1.25%) (Table 2). In 28 patients (8.78%), an association of medications was required to achieve an adequate level of sedation. Of these, 19 patients received midazolam and ketamine, 3 patients received midazolam and sodium thiopental, and 6 patients were sedated with midazolam, ketamine and sodium thiopental.

Comparing patients with and without chronic home therapy, no differences were identified in the necessity for sedation (chi square test $p = 0.85$). In the study population, 181 patients (69.08%) had a history of psychiatric comorbidities and 70 (52.63%) were treated with chronic psychiatric drugs. Adjusting the administration of ketamine, with or without psychiatric home therapy, and psychiatric comorbidities, an OR of 48.18 (9% CI: 18.21–143.55) was found.

Intubation or bag-valve-mask ventilation was never required, neither in the prehospital setting nor in the ED, all patients received oxygen (O$_2$) support with a mean FiO$_2$ of 0.24 (SD ± 0.1) through a Venturi face mask. A FiO$_2$ >0.21 was required in 40 patients (12.5%) and a FiO$_2$ ≥0.40 was necessary in 35 patients (11%), only 1.25% of patients received a FiO$_2$ of 1.0 (Fig. 2). Wilcoxon rank sum test with continuity correction showed a strong correlation ($p < 0.001$) between patients who received more than one sedative
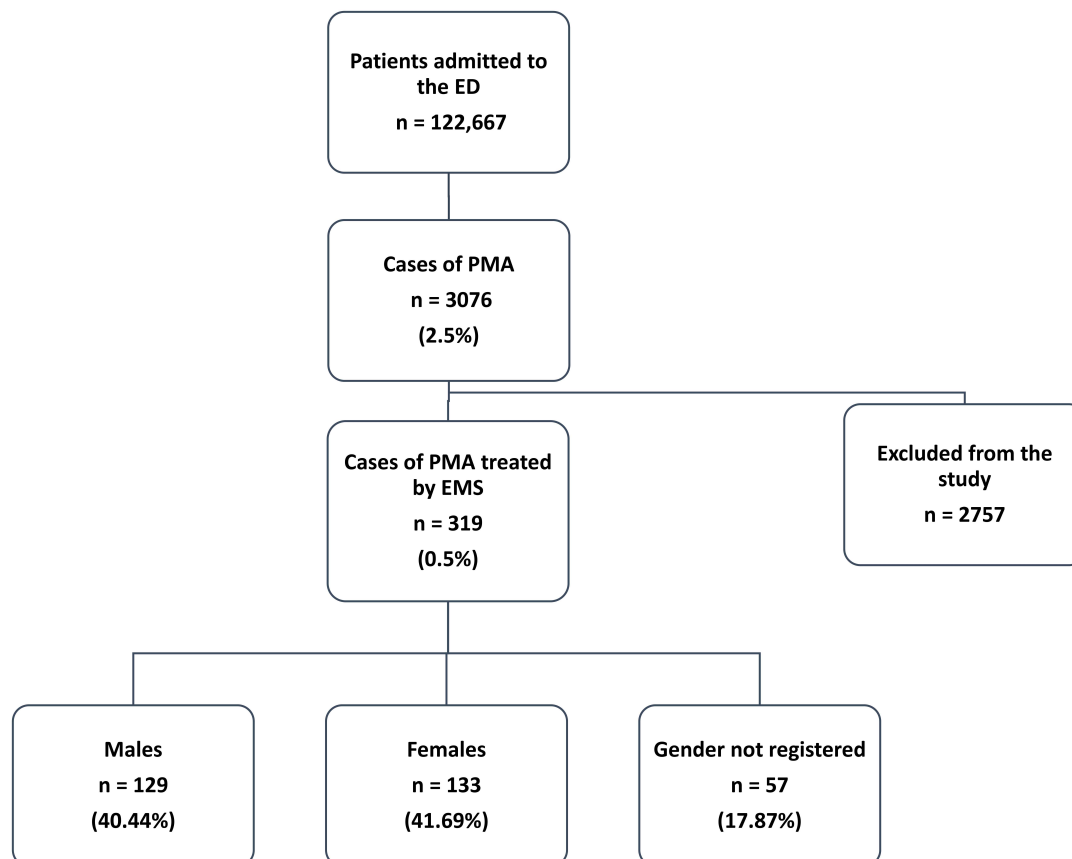
FIGURE 1. Patients enrolled in the study. n, number; ED, Emergency Departments; PMA, Psychomotor Agitation; EMS, Emergency Medical System.

TABLE 1. Demographic data, patient characteristics and principal comorbidities.

Patients	Number	(%)	Mean
Females	133	41.69	
Males	129	40.44	
Gender not registered	57	17.87	
Number of comorbidities	233	88.93	
Comorbidities:	204	77.86	
Cardiovascular	58	22.14	
CNS	13	4.96	
Respiratory	7	2.67	
Psychiatric	181	69.08	
Renal	6	2.29	
Neoplastic	5	1.91	
Metabolic	28	14.50	
Other	65	24.90	
Unknown	29	11.07	
Psychiatric Therapy	148	56.49	
Age			50.7 years (SD ± 20.7)
LOHS			2.5 days (SD ± 5.5)

CNS, central nervous system; LOHS, length of hospital stay; SD, standard deviation.

T A B L E 2. Sedative drugs for PMA expressed in milligrams (mg).

Medication	IV	Mean dose	IN	Mean dose	IM	Mean dose	OS	Mean dose
Midazolam (19.75%)	66.6% (47)	5.7	31.7% (24)	9.4	14.5% (9)	6.9	3.2% (2)	12.5
Ketamine (9.09%)	41.4% (12)	94.6	-	-	62.1% (18)	101.1	-	-
Diazepam (6.58%)	52.4% (11)	8.2	-	-	4.8% (1)	10.0	47.6% (10)	3.7

IV, intravenous; IN, intranasal; IM, intramuscular; OS, oral.
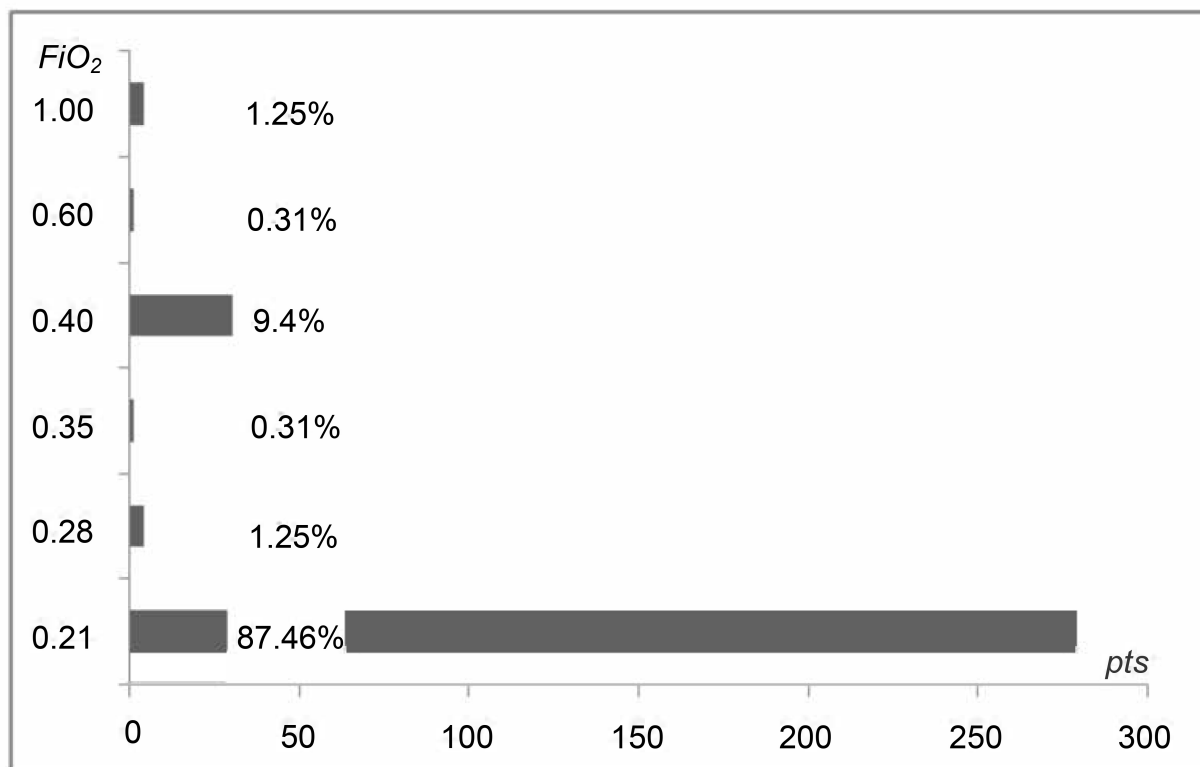
F I G U R E 2. Distribution of patients (pts) with different inspiratory oxygen fractions (FiO$_2$) trough Venturi face mask.

drug and the need for oxygen therapy (FiO$_2$ >0.21) (Fig. 3). Regardless of the route of administration, intramuscular (IM) or intravenous (IV), ketamine was significantly associated with the requirement of FiO$_2$ $\geq$0.4 through a Venturi face mask ($p < 0.001$). This was seen in univariate analysis (chi-squared test and Wilcoxon Mann Whitney test—mean FiO$_2$ 0.21 *vs.* 0.40—median FiO$_2$ 0.21 *vs.* 0.40) and Multiple Logistic regression (FiO$_2$ $\geq$0.4) analysis with an OR of 61.35 (95% CI: 23.13–183.82).

Statistically significant differences were found in FiO$_2$, considered both as continuous variable and dichotomous variable (FiO$_2$ $\geq$0.4) due to midazolam use. FiO$_2$ requirements were higher in patients with midazolam administration ($p < 0.001$—mean FiO$_2$ 0.33 *vs.* 0.22). This was observed in univariate analysis (Chi squared test and Wilcoxon Mann Whitney test) and Multiple Logistic regression (FiO$_2$ $\geq$0.4) where we obtain an OR of 17.58 (95% CI 7.86–42.67) adjusted for home therapy and an OR of 14.23 (95% CI: 6.33–34.75) adjusted for home therapy and psychiatric comorbidities. As shown in Table 2, midazolam was more frequently used for sedation and

the most common route of administration was IV, but IN, IM and OS routes were also used. The mean dose received by the patients considering all routes of administration was 5.5 mg (ranging from 2 to 20 mg). In the population examined, the mean transfer time from the target to the hospital was 20 minutes, time in which the sedatives were administrated. Midazolam IV was usually administered in repeated boluses of 2 mg, for the other routs it was administered in a single bolus.

The mean LOHS was of 2.5 days (SD $\pm$ 5.5), with 190 patients (71.16%) that stayed less than one night at the hospital. As shown in Fig. 4, patients with a specific psychiatric therapy had a longer LOHS ($p = 0.004$). A statistically significant difference in LOHS was observed in patients treated with IV ketamine, considered both as a continuous variable (mean: 2.48 *vs.* 2.66, $p = 0.03$) and dichotomous variable ($\geq$24 h, $p = 0.04$). Considering multiple logistic regressions, a statistically significant correlation was observed between psychiatric home therapy and LOHS ($\geq$24 h) adjusted for ketamine IV administration ($p = 0.05$), with an OR of 1.79 (95% CI: 1.01–3.26) and adjusted for ketamine administration with or without
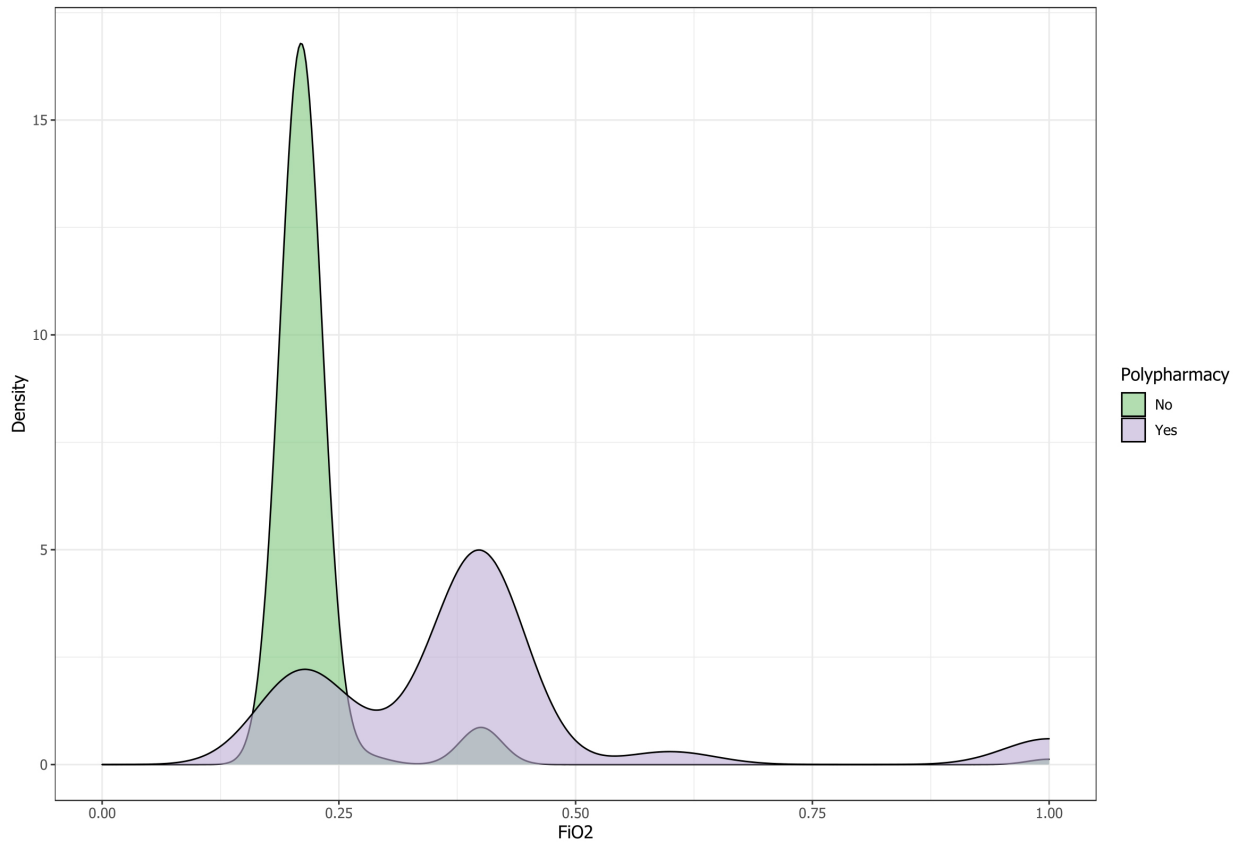
F I G U R E 3. Need of oxygen therapy in sedated patients. Higher FiO_2 is required for patients who received more than one sedative (purple color) to reach adequate sedation ($p < 0.001$). FiO_2, inspiratory oxygen fraction.
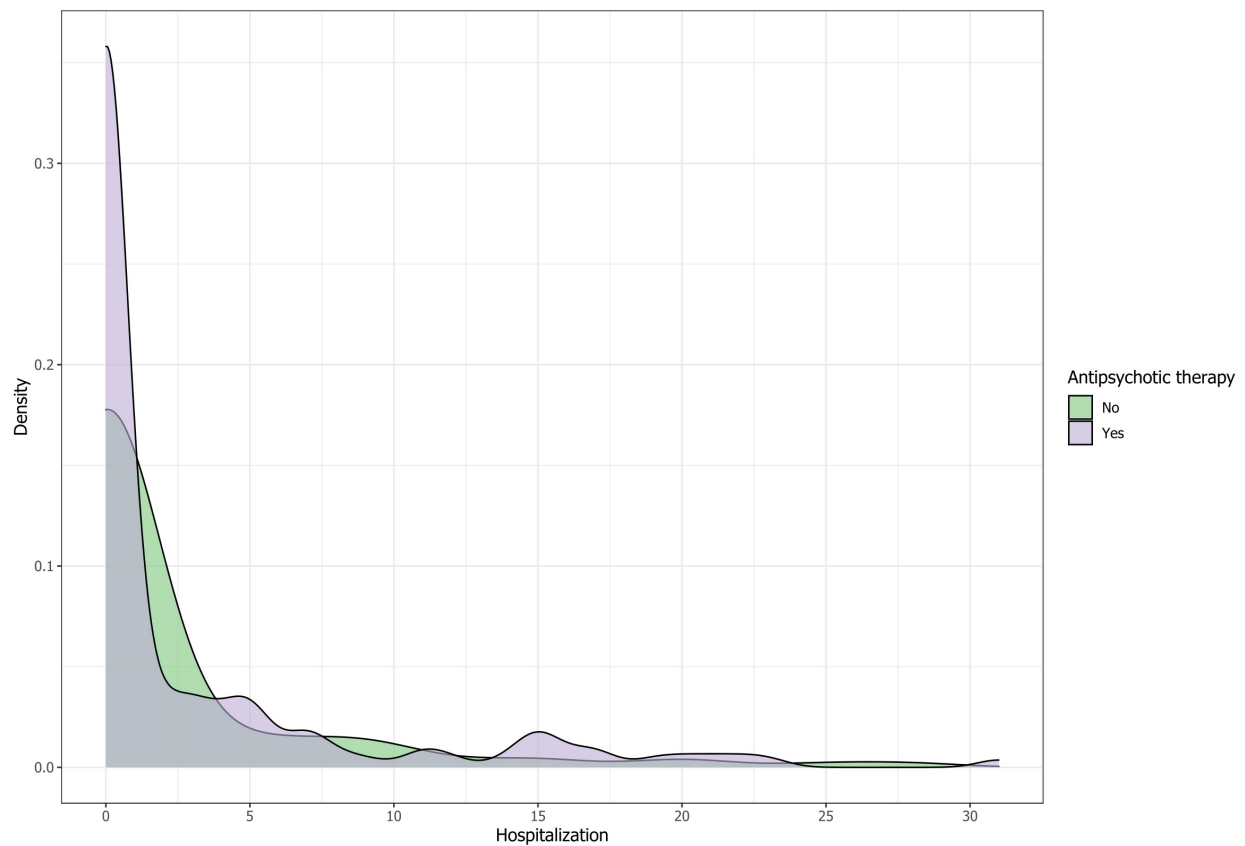

F I G U R E 4. Patients with antipsychotic therapy (in purple; n = 148; 56.49%) needed longer hospitalization ($p = 0.004$).

psychiatric comorbidities ($p = 0.045$) with an OR of 2.27 (95% CI: 1.04–5.22) in case of psychiatric comorbidities and home therapy. Midazolam showed a statistically significant difference for LOHS, considered both as a continuous variable ($p = 0.045$) and dichotomous variable (≥ 24 h) ($p = 0.03$), with a longer LOHS in case of its use. This correlation was also statistically significant regardless of the route of administration ($p = 0.04$). Considering multiple logistic regressions, we observe a statistically significant correlation between midazolam use and LOHS (≥ 24 h) adjusted with home therapy ($p = 0.03$), with an OR of 1.95 (95% CI: 1.06–3.55) and adjusted with or without home therapy and psychiatric comorbidities ($p = 0.04$) with an OR of 2.32 (95% CI: 1.07–5.34).

A statistically significant difference in FiO_2 and LOHS was found, considered both as a continuous variable and dichotomous variable due to the administration of more than one sedative ($p < 0.005$). No ADRs or ExDS were observed.

4. Discussion

This retrospective cohort study found a prevalence of PMA of 2.5%, and a prevalence of PMA managed by the out-of-hospital ground EMS of 0.5%. These results are consistent with the existing literature [4].

In 23 patients (7.21%) verbal de-escalation techniques were used. As reported in the literature, different techniques can be used to obtain comfort measures, for example offering a safe or quiet location, dimming the lights, and adjusting the temperature. It is important to evaluate the patient's cooperation level to decide on a medical upgrade [8–10].

In the study population, no patients had the necessity of physical restraints. The use of these devices has declined over the past decades as a result of adverse outcomes such as strangulation, asphyxiation, compromised circulation of the extremities, and chest compression. It should be reserved for patients who remain a danger to themselves or others [11]. If verbal de-escalation is ineffective, medications may be required.

Many routes of administration can be chosen according to circumstances and clinical evaluation of the patients. Short-acting benzodiazepines, such as midazolam, are widely used because of their rapid onset time [12].

Benzodiazepines are drugs that act on the ionotropic gamma-aminobutyric acid type A ($GABA_A$) receptors in the central nervous system. These drugs do not activate $GABA_A$ receptors directly but they require GABA. The main effects of benzodiazepines are hypnosis, anterograde amnesia, sedation, decreased anxiety, centrally mediated muscle relaxation and anti-convulsant activity.

As main side effects benzodiazepines have a dose-dependent ventilatory depressant effect and they also cause a modest reduction in arterial blood pressure, with a synergistic interaction with other hypnotic drugs and opioids. There are four benzodiazepines used in the emergency settings: midazolam, diazepam and lorazepam and the antagonist flumazenil. Midazolam has the shortest recovery profile and can be administered by all routes [13].

This study showed that intranasal (IN) midazolam (2–10 mg) was preferred in 31.7% of the situations. In fact, unlike the IV route, IN route administration does not require a sterile preparation or access site. Using both nostrils optimizes medication delivery because only a limited volume can be administered in a single nostril.

Another valid and safe drug to control PMA is ketamine, a sedative agent that works by interacting with a variety of receptors, including N-methyl-D-aspartate, nitric oxide synthase, and multiple opioid receptors. Ketamine is a dissociative agent which causes a trance-like state resulting in analgesia and amnesia and it has recently been proposed as a treatment for agitation [14]. Ketamine has an onset of action within 3 minutes with a duration of effect ranging from 5–30 minutes [15]. Therefore, if ketamine can rapidly sedate these patients, it may curb or prevent the complications of ExDS [16]. A total of 29 (9.09%) patients have been treated with ketamine. 12 of these cases (41.37%) received an intravenous administration (mean dose: 94.62 mg), 23 patients needed oxygen supply, and 3 a FiO_2 higher than 0.4; no one required intubation or bag-valve-mask ventilation, neither in the prehospital setting nor in the ED.

A recent meta-analysis found an intubation rate of 30.5% (95% CI: 27.0–34.1) in patients that received ketamine from the paramedics during ground transport and intubated at the arrival in the ED [17]. Some authors stated that higher doses of ketamine are associated with an increased frequency of intubation. Although they describe an association between ketamine dose, intubation, and hospital admission, their data do not establish causality [18, 19]. In Burnett's study, 29% of patients who received IM ketamine for prehospital pharmacological restraint were ultimately intubated in the ED and none by EMS providers in the prehospital setting [18].

A significant decrease in oxygen saturation after ketamine administration was seen in the prehospital setting in a case series reporting the treatment of 13 patients: 3 developed severe hypoxia and 2 required intubation [20]. In our study, observing patients who received FiO_2 0.4, we obtain an OR of 61.35 adjusted for psychiatric home therapy and an OR of 48.18 adjusted for psychiatric comorbidities and home therapy, suggesting a relevant effect on the respiratory system, especially in those patients. As reported in the literature by Cole *et al.* [21], many patients who received ketamine were intubated for hypersalivation (16%), apnea (12%), aspiration/vomiting (12%), laryngospasm (8%), seizure (4%), and traumatic injuries (4%) [21]. These complications were not seen in this study population and no patient was intubated and mechanically ventilated.

The mean length of hospital stay reported in a Spanish study was 21.8 days [22]. In another study conducted by Cots *et al.* [23], admissions were significantly longer among patients with a diagnosis of agitation: 12 ± 11.5 days. We reported a total LOHS of 2.5 days (SD $\pm$ 5.5); in the study, only 77 (28.8%) patients required hospitalization with a mean LOHS of 8.66 days (SD $\pm$ 7.19). We hypothesize that the patients in our cohort experienced a shorter LOHS maybe because of a mild sedation that avoided acute complications and that did not require advanced airway management with intubation and intensive care unit admission. Patients were promptly taken in charge by a psychiatrist, rapidly discharged if stable and entrusted to territorial psychiatric service.

A subgroup analysis was carried out, evaluating the LOHS of patients with antipsychotic home therapy and a known diagnosis of psychiatric comorbidity who received ketamine or midazolam. In the ketamine subgroup, an OR of 1.79 (*p*: 0.045) for patients with antipsychotic home therapy and an OR of 2.27 with antipsychotic therapy and psychiatric comorbidities were found. Similarly, midazolam administration led to a longer hospital stay (more than 24 hours) regardless of the route of administration (IN or IV) (*p*: 0.04), especially in those patients treated with antipsychotic home therapy (OR: 1.95). Psychiatric patients with specific home therapy and sedated with midazolam had an OR of 2.32.

5. Limitations

Our sample may have underestimated the real incidence of PMA as we only enrolled the patients transported to the hospital and treated by ground EMS, potentially missing patients that reached the ED in other ways (police, relatives, friends and acquaintances).

6. Conclusions

Psychomotor agitation has been confirmed as a widespread and frequent event in prehospital settings, requiring rapid assessment and management. Therapeutical strategies should include verbal de-escalation, pharmacologic interventions with benzodiazepines, ketamine, and rarely associations of drugs. The use of these drugs in the agitated patient in the prehospital setting is safe, does not increase hypoxia, intubation rate, or adverse drug reactions.

AVAILABILITY OF DATA AND MATERIALS

Upon request.

AUTHOR CONTRIBUTIONS

ST, GT and TB—designed the research study. EF and EQ—performed the research and data collection. AT—analyzed the data. ST, FM, CM and TB—wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the regional Ethics Committee of Friuli-Venezia Giulia (CEUR FVG) in September 2019, protocol number #2953. Given its retrospective nature, patient consent was waived, but the European Privacy Regulation 2016/679 on General Data Protection Regulation was respected.

ACKNOWLEDGMENT

Not applicable.

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