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Original article

The efficacy and safety of procedural sedoanalgesia performed by emergency physicians in the emergency department of Piacenza. A single-center retrospective observational study

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Abstract. Procedural sedation (PSA) is a common procedure performed in the emergency department (ED) and represents a fundamental skill for emergency physicians (EP). However, only a few studies have looked at the overall success and incidence of complications of PSA administered by non-anesthesiologists. This study aims to examine the effectiveness and safety of PSA administered by EPs in the ED. *Methods:* This is a single-center retrospective observational study of patients undergoing PSA in the ED of Piacenza (Emilia-Romagna, Italy) between January 1, 2022, and May 21, 2023, for electric cardioversion, bone dislocation or fracture reductions, and pacing. Patients' demographic data, nil *per os* time, doses and combination of drugs, vital signs, and incidence of adverse events (AEs) were recorded. *Results*: Three hundred and seventeen patients were enrolled. The most often used intravenous (IV) combination was fentanyl plus midazolam (45%), followed by midazolam alone (41%). In 314 patients (99%), PSA was successfully provided. AEs occurred in 28 out of 317 patients (8.5%). The most common complication was hypoxia (3.1%). No patient required intubation. All the AEs have been successfully managed by EPs. No deaths were recorded. *Conclusions:* Our results indicate that EPs can safely and effectively administer PSA in the ED. We suggest the creation of an Italian SPA registry to promote collaboration amongst Italian EDs and the sharing of drug protocols to standardize patients' pathways. (www.actabiomedica.it)

Key words: emergency medicine, procedural sedation, propofol, analgesia

Introduction

Procedural sedoanalgesia (PSA) is routinely used in the emergency department (ED) to facilitate potentially painful procedures, including electric cardioversion (ECV), pain management of bone fractures or dislocation reduction, abscess drainage, and lumbar puncture by alleviating pain, anxiety, and suffering (1, 2). PSA involves the use of short-acting analgesic and sedative medications to enable emergency physicians (EPs) to perform procedures effectively and requires close monitoring of the patient for potential adverse effects (AEs). Currently no guideline for PSA exists in Italy. 2014 Italian Intercompany Recommendations (SIAARTI, SIMEU, SIS 118, AISD, SIARED, SICUT, IRC) on emergency pain management state that 'As a rule, non-anaesthesiologists should be limited to conscious sedation techniques. Over the last few decades, there has been significant growth in the ED management of PSA, although the growth of EPs in this field depends on themselves and their ability to demonstrate solidity and mastery of their context.

As a result, varying aspects of PSA within the emergency setting remain controversial in Italy nowadays. Disagreement persists regarding the management of deeper levels of sedation by EPs and the appropriateness of their credentialing for specific PSA agents. When performed by trained EPs, PSA has been demonstrated to be safe (3-6). Moreover, we have the requisite skill sets for ventilation, airway management, and resuscitation to provide safe patient care in the case of an adverse event. Expertise in PSA is included as a core competency in emergency medicine (EM) residency programs and EM fellowships (2). The use of various analgesic, sedative, and anaesthetic agents has been outlined in several guidelines (7-8). Numerous classes and combinations of drugs are commonly used for PSA in the ED (9-16). The use of short-acting sedative agents such as propofol (9, 11-13), etomidate (15) and ketamine (9, 10, 12, 14) for example, has gained widespread acceptance. The American College of Emergency Physicians (ACEP) has developed a clinical policy regarding PSA (2). AEs reporting for PSA, however, have been heterogeneous. Bellolio MF et al. (17) conducted a systematic review and meta-analysis to evaluate the incidence of adverse events (AEs) in adults undergoing procedural sedation in the ED. The most frequent events were hypoxia, vomiting, hypotension, and apnea. Hypoxia occurred in 40.2 per 1,000 sedations (95% CI = 32.5 to 47.9); vomiting in 16.4 per 1,000 sedations (95% CI = 9.7 to 23.0); hypotension in 15.2 per 1,000 sedations (95% CI = 10.7 to 19.7); and apnea in 12.4 per 1,000 (95% CI = 7.9 to 16.9). The incidence of severe AEs requiring emergent interventions such as laryngospasm, intubation, or aspiration was low. Cases of death were not reported. Severe AEs requiring emergent medical intervention were infrequent, with one case of aspiration in 2,370 sedations (1.2 per 1,000), one case of laryngospasm in 883 sedations (4.2 per 1,000), and two intubations in 3,636 sedations (1.6 per 1,000). These results are similar to previous studies, which found that respiratory events leading to major adverse outcomes, such as aspiration, unexpected intubation, or cardiac arrest, were extremely infrequent (18-19). Given the frequent use of PSA by EPs, as well as the continued development of research and clinical evidence for this practice, we conducted a single-center retrospective study to determine the efficacy and safety of PSA in our ED (Guglielmo da Saliceto Hospital, Piacenza, Emilia-Romagna, Italy), including the incidence and the frequency of AEs for each drug and different drug combinations.

Aim of the study

To investigate the efficacy and safety of PSA performed in the ED of Piacenza (Emilia-Romagna, Italy) by EPs for electric cardioversion, bone dislocation or fracture reductions, and pacing.

Materials and Methods

All patients who presented to the ED of Guglielmo da Saliceto Hospital of Piacenza between January 1, 2022, and May 21, 2023, requiring PSA were retrospectively evaluated. Our ED is a tertiary care center that evaluates and manages more than 150,000 patients each year. Patients who received sedative, dissociative, or analgesic agents for endotracheal intubation, pain control without an associated procedure, muscle relaxation, seizure control, or end-of-life care were excluded. The treating EP in the ED was responsible for determining the agents used for PSA. All patients signed a written informed consent for PSA. For each patient who required PSA, sedation data were retrospectively completed. Data included the patient's age, sex, American Society of Anesthesiologists (ASA) class, history of allergies, weight, medical history, and the number of hours since the patient's last oral or gastric intake (NPO). In accordance with current ED policy, patients generally did not receive PSA until at least 3 hours had passed since their last oral or gastric intake. The use of premedication with IV fluids and supplemental oxygen from the beginning was recorded.

PSA were performed by an EM attending physician or fellow. All fellows and residents received extensive instruction in PSA and were directly supervised by attending EPs. The EP administering the medications was not the same physician performing the procedure. The training level of the provider of PSA was not recorded or analysed, but at least one EP engaged

in the procedure had expertise in PSA conduction and airway management, as required by ACEP (2). During the sedation and procedure, the following vital signs were recorded at 5-minute intervals: respiratory rate, blood pressure, and level of consciousness. Oxygen saturation and the electrocardiogram trace were recorded continuously. Since our ED had not yet introduced end-tidal CO2 monitoring, it was not utilized. The type, route, and amount of medication given to the patient were recorded. The success of sedation was defined *a priori* as the successful completion of the procedure in a minimally responsive subject. For example, in a patient who was to receive PSA for fracture reduction, the fracture would be manipulated to determine if he or she was adequately sedated to enable the procedure to begin. If the patient's level of consciousness did not change during the procedure or if the patient moved minimally during the procedure, PSA was considered successful. AEs were noted in the clinical records and therefore collected. AEs were defined *a priori* as follows: persistent oxygen desaturation to less than 93% on pulse oximetry and requiring supplemental oxygen; apnea; dizziness; laryngospasm; arrhythmias; hypotension; nausea; vomiting; and aspiration. AEs were subsequently stratified according to the level of intervention needed as follows:

1. Minimal interventions: agitation not requiring any intervention; vomiting without inhalation; hypotension not requiring any intervention.
2. Minor interventions: airway obstruction resolved after stimulation; airway obstruction resolved after airway repositioning; apnea resolved after stimulation; hypoxia resolved after stimulation or airway repositioning or oxygen administration.
3. Moderate interventions: airway obstruction resolved with oral airway insertion; apnea or hypoxia resolved with bag valve mask ventilation; hypotension resolved after fluid bolus.
4. Severe intervention: aspiration; unplanned intubation; or RCP following cardiac arrest.

Other reactions regarded by the EP administering PSA to be AEs were recognized and recorded. The EP in charge of the PSA made decisions about interventions for AEs. The use of supplemental oxygen during PSA was considered the standard of care at our institution during the study. As a result, all patients received supplemental oxygen before and during the treatment.

Clinical and demographic data are presented as mean (+/- SD), median, ranges, and proportions. The success of PSA and the incidence of AEs are presented as proportions. If we denote with θ the complication rate, we test the hypothesis H_θ: $\theta \geq \theta_0$ using a one-sided binomial test. $\Theta_0 = 0.01$ is the reference literature.

Results

PSA were performed in 317 patients. The median age of the patients was 63 years (mean [SD], 18.9 (66) years. Ninety-four patients (29.9%) were older than 76 years, 76 (23.9%) were between 66 and 76, 70 (22%) were between 54 and 66 and 77 (24.2%) were younger than 54. There were no significant differences among age groups in regard to the likelihood of a failed sedation. Most of the patients (195, 61.5%) were men. 19.5% of the patients were ASA class I; 61.8% were class II; 16% were class III; and 2.7% were class IV. 314 patients (96.1%) waited at least 3 hours since the last NPO before receiving sedation. PSA was performed 1 hour after the last NPO in 3 patients (0.9%) due to an emergent scenario, including an unstable ventricular tachycardia in one case and two cases of peri-arrest in a III-grade AV block requiring pacing (Table 1).

Most of the patients (72.5%) required PSA for ECV, 25.8% for the reduction of a fracture or a bone dislocation, and 1.7% for pacing for a III-degree AV block. The type and frequency of use of various PSA regimens are shown in Figure 1.

All the drugs were administered intravenously (IV), except for MEOPA (nitrogen monoxide-oxygen mixture). The most commonly used combination was fentanyl and midazolam (46.3%), followed by midazolam (41.9%) and midazolam plus morphine (5.5%). Fourteen patients (4.5%) received propofol, 3 patients (0.9%) propofol and midazolam, one patient (0.3%) propofol and fentanyl, 2 patients a combination of > 2 drugs: 1 patient (0.3%) a combination of midazolam, fentanyl and MEOPA for a dislocated shoulder,

Table 1. Comparison of general characteristic and incidence of complications noted during PSA.

Characteristic (N = 317)	Median (IQR) or N (%)	Complication Group (N = 28)	No Complications Group (N = 289)
Sex (Female / Male)	122 (38.5%)/195 (61.5%)	12 (42.8%)/16 (57.2%)	110 (38%)/179 (62%)
Age (y)	63 (44-81)	69.5 (55.5-83.5)	62 (43-81)
Q1 (12-54)	77	2 (14.6%)	75 (25.9%)
Q2 (55-66)	70	6 (21.4%)	64 (22%)
Q3 (67-76)	76	9 (32%)	67 (23.1%)
Q4 (77-94)	94	9 (32%)	85 (29%)
Weight (kg)	70.7 (77.7-64.7)	69.7 (67-72.4)	70.7 (77.7-64.7)
ASA class			
I	62 (19.5%)	1 (3.5%)	61 (21.1%)
II	196 (61.8%)	21 (75%)	175 (60%)
III	51 (16%)	6 (21.5%)	45 (15.5%)
IV	8 (2.7%)	0	8 (3.4%)
Mean NPO (hours)	3 (2.7-3.3)	3 (2.8-3.2)	3 (2.8-3.2)
Procedures			
Electric cardioversion	230 (72.5%)	24 (85.7%)	206 (71.2%)
Dislocation or fracture reduction	82 (25.8)	4 (14.3%)	78 (26.9%)
Pacing	5 (1.7%)	0	5 (1.9%)
Agent(s)			
Midazolam and Fentanyl	146 (46.3%)	15 (53.6%)	131 (46.4%)
Midazolam	131 (41.9%)	10 (35.8%)	121 (41.8%)
Midazolam and Morphine	17 (5.5%)	1 (3.5%)	16 (5.8%)
Propofol	14 (4.5%)	1 (3.5%)	13 (4.4%)
Propofol and Midazolam	3 (0.9%)	1 (3.5%)	2 (0.7%)
Midazolam, Fentanyl and Nitrous oxide	1 (0.3%)	0	1 (0.3%)
Propofol, Midazolam and Fentanyl	1 (0.3%)	0	1 (0.3%)
Propofol and Fentanyl	1 (0.3%)	0	1 (0.3%)

Abbreviations: Q = quartile range; NPO = nil per os.

and one patient (0.3%) a combination of propofol, midazolam and fentanyl for an exposed fracture reduction. Table 2 shows the range of doses utilized for each medication per kilogram of body weight within a sedation regimen, which is part of the local ED guidelines for PSA.

During PSA, 307 (96.9%) patients reached a level of consciousness of 3 (asleep and unarousable) on a 3-point scale, 7 (2.8%) reached a level of consciousness of 2 (drowsy or asleep but arousable), and 3 (0.9%) remained awake during PSA. PSA was successful in 314/317 (99%) procedures, with the exception of 3 (0.9%) patients who received fentanyl alone for fracture reduction and were premedicated with analgesics. The mean (SD) NPO of the 3 patients who received fentanyl alone before sedation was 1 hour (SD 0.33) (median 1 hour; range, 1-2 hours). Antidotes for PSA were given to 184/317 (58%) patients in order to shorten the monitoring period. Flumazenil was administered to 163 (51.4%) patients, whereas naloxone and flumazenil were administered to 21 (6.6%) patients. As shown in Figure 2, AEs occurred in 28/317 (8.5%)

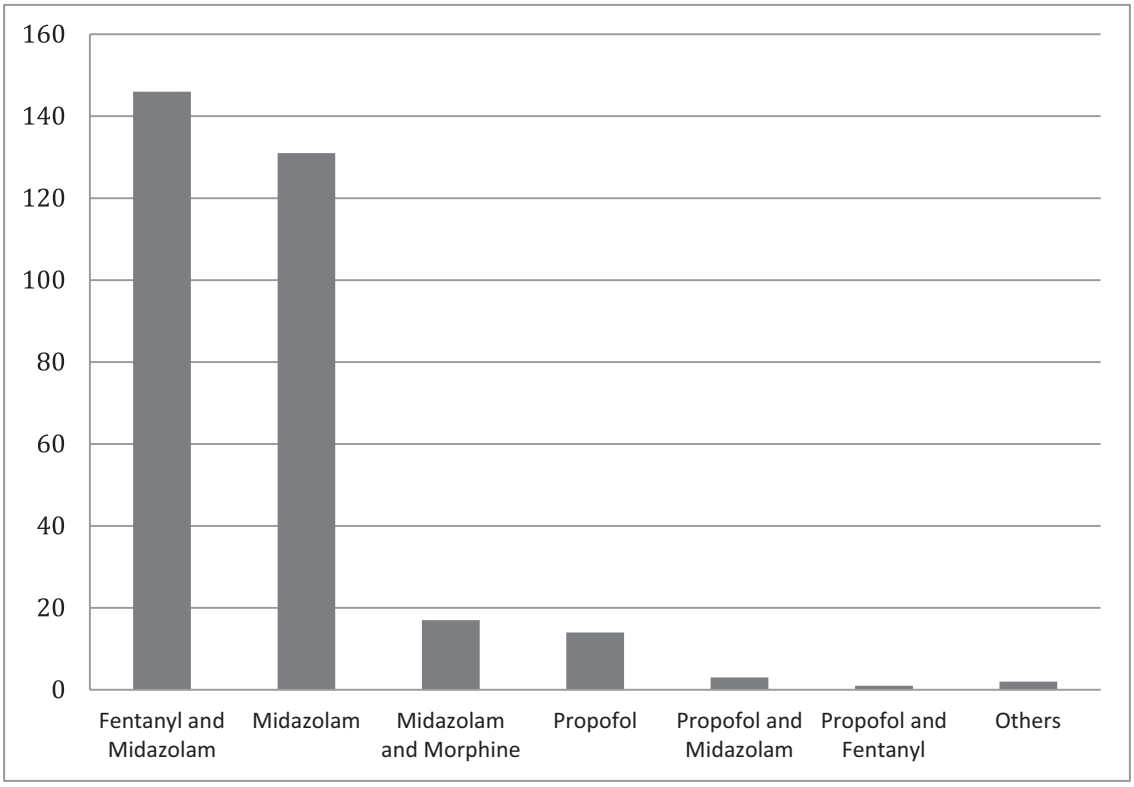

Figure 1. Type and frequency of use of PSA regimens. Others: combination of > 2 drugs.

of the patients. The most common events were hypoxia (10/317 patients, 3.1%), followed by apnea (9/317 patients, 2.8%). No patient required endotracheal intubation. One patient (0.3%) who was sedated with fentanyl and midazolam required an oral airway placed for hypoxia caused by an apparent upper airway obstruction. One patient (0.3%) who received morphine and midazolam was treated with IV metoclopramide for vomiting. As a minor intervention, nine patients (2.8%) required supplementary oxygen after PSA for hypoxia. Fourteen patients (4.4%) required the following moderate interventions: 7 patients (2.2%) received bag-valve-mask ventilation, 5 (1.5%) patients received a supplemental fluid bolus due to hypotension, one patient (0.3%) had an oral airway placed due to airway obstruction, and one patient (0.3%) received flumazenil due to apnea.

Patients sedated with fentanyl plus midazolam who developed AEs received a larger dose of midazolam (0.13 mg/kg versus 0.09 mg/kg) than those who did not. There was no significant difference in weight or mean NPO time between patients who experienced AEs and those who did not. Patients who experienced AEs were more likely to be female (42%) and older (median 69.5 vs 63 years). Patients who received PSA for ECV and pacing were more likely to have an AE than those who had PSA for bone fracture or dislocation reduction (26% vs 14%, respectively). If we consider the type of PSA, patients sedated with fentanyl and midazolam had a higher rate of AEs (15/146, 10.2%) than patients sedated using midazolam alone, midazolam and morphine, or propofol alone (10/131, 7.6%; 1/14, 7.1%; and 1/17, 5.8%, respectively). When the patient's age was considered, patients in the 4th interquartile range of age (> 76 years old.) were more likely to develop complications than patients in the youngest age group (32% vs 14.6%). There were no differences in mean NPO time between age groups. Patients in the youngest group were more likely to be ASA class I than the other age

Table 2. Comparison of PSA regimens and incidence of complications noted during PSA.

Group	Total Sedations	Complication	no.	Medication	Mean Dose (SD)	Medication	Mean Dose (SD)
Midazolam and Fentanyl	146	yes	15	Fentanyl	0.90 (0.46)	Midazolam	0.13 (0.07)
		no	131		0.79 (0.42)		0.09 (0.44)
Midazolam	131	yes	10	Midazolam	0.13 (0.55)		
		no	121		0.12 (0.44)		
Midazolam and Morphine	17	yes	1	Midazolam	NA	Morphine	NA
		no	16		0.079 (0.3)		0.077 (0.05)
Propofol	14	yes	1	Propofol	NA		
		no	13		1.26 (0.69)		
Propofol and Midazolam	3	yes	1	Propofol	NA	Midazolam	NA
		no	2		NA		NA
Midazolam, Fentanyl and MEOPA	1	yes	0		NA		
		no	1		NA		
Propofol, Midazolam and Fentanyl	1	yes	0		NA		
		no	1		NA		
Propofol and Fentanyl	1	yes	0		NA		
		no	1		NA		

Abbreviations: NA = not applicable.

groups (79.0% vs 4.8%, 4.8% and 11.4%). Patients in the youngest age group were also less likely to experience an AE than patients in both other age groups (2.5% vs 8.5%; 2.5% vs 9.2%; and 2.5% vs 11.7%). Patients in the youngest age groups were more likely to be male than both other age groups (87.4% and 75.7% for I and II quartiles respectively vs 46% and 42.5% for III and IV quartiles). Within each sedation regimen, no difference was found between patients who experienced a complication and those who did not in regard to mean age and sex. Finally, the number of observed major AEs is 0. As under the null hypothesis the number of complication cases is distributed as Binom (x,n = 317, θ_0 = 0.01), the p-value of our one-sided test is given by $P(x = 0|n = 317, \theta_0 = 0.01) = 0.041$. The null hypothesis can therefore be rejected at the 0.05 significance level.

Discussion and Conclusion

Our study aims to document the success of PSA and the incidence of AEs in patients undergoing PSA in an ED where PSA is primarily performed by residents, EM fellows, or attending physicians. In our study population, 99% of patients were successfully sedated, and 8.5% experienced a PSA-related AE. Most of the patients (10/28, 35.7%) had hypoxia that responded immediately to supplemental oxygen therapy; 9 patients (2.8%) had apnea, but only 1 required an oral airway; 7 patients required bag-valve mask ventilation for hypoxia; 5 (1.5%) patients received a supplemental fluid bolus due to hypotension; and one patient required the use of a reversal due to apnea. The remaining AEs were considered minor and were easily managed by EPs. Therefore, PSA was provided safely and efficaciously by EPs. However, it should be recognized that the low number of AEs noted in our study was achieved by trained EPs with advanced skills in assessing unstable vital signs and maintaining airways in emergencies. Furthermore, all the EPs use the indications stated in the local guide for PSA. This could explain the reason why the complication rate is lower than that reported in previous studies. Moreover, evidence shows that the incidence of AEs is dose-dependent, and despite the availability of antidotes, it should be kept in mind

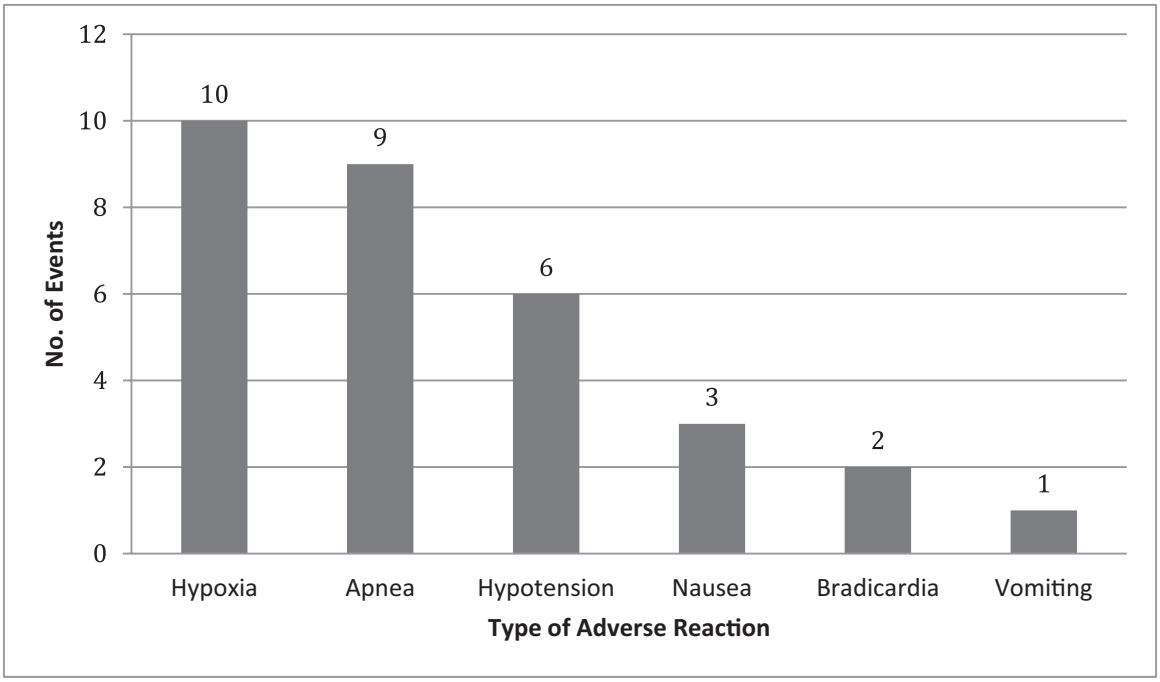

Figure 2. Number and type of AEs noted during and soon after PSA.

that they are not free from complications. Therefore, it is mandatory to point out the importance of using the correct dosages. Bellolio MF et al. conducted a systematic review and meta-analysis to evaluate the incidence of adverse events in adults undergoing PSA in the ED. The authors included RCTs and observational studies published after 2005 in which PSA was used in adult patients in the ED. A total of 9,652 procedural sedations were included. The most frequent events were hypoxia, vomiting, hypotension, and apnea. Hypoxia occurred in 40.2 per 1,000 sedations (95% CI = 32.5 to 47.9); vomiting in 16.4 per 1,000 sedations (95% CI = 9.7 to 23.0); hypotension in 15.2 per 1,000 sedations (95% CI = 10.7 to 19.7); and apnea in 12.4 per 1,000 (95% CI = 7.9 to 16.9). However, the medications used for PSA in these studies were different from those used in our study. Our lower complication rate may be due to the fact that this was a retrospective study, and therefore some minor complications may have been missed in the clinical report. Interestingly, since the number of observed major complications is 0, we may conclude that PSA performed by EP is a safe procedure. Another limitation of this study is the little use of ketamine combined with propofol (ketofol) for procedural sedation: since one of the most frequent AEs is respiratory depression, it might be useful, when possible (therefore not in ECV), as an improvement proposal for the future (27). In addition, although statistically significant findings were found among patients who did and did not experience a PSA-related AE, some findings were not proven to be significant. Since significant findings most likely occurred as the result of the large numbers of patients studied, allowing for small differences between groups to become statistically, our findings may be limited by the small subgroups of patients. A second limitation of our study is that patients were not randomized to receive the PSA regimens, potentially biasing comparisons among groups of subjects receiving differing regimens. Finally, variability among various EPs may have existed as to what constitutes an AE, inflating or deflating the reported rate. In summary, before doing PSA, the EP should inform the patient about the procedure's risks, advantages, and alternatives, as well as the scheduled sedation. Successful performance requires recognition not only of the pitfalls associated with the medications, but also consideration for the complexity of the patient's underlying physiology and the degree of illness or injury. Patients who receive PSA in the ED

are at increased risk of complications due to the emergent nature of their conditions that brought them to the ED and the need for pain and anxiety management to properly accomplish an intervention or diagnostic procedure. The high-risk nature and comorbidities in these patients may include cardiopulmonary disorders, multiple traumas, head injury, or intoxication (1). Detectable respiratory events such as hypoxia and apnea are common during PSA and may be precursors of more serious events (20). To further minimize these AEs, the routine use of capnography monitoring during PSA has been recommended, as capnography detects hypoventilation and apnea earlier than pulse oximetry and/or clinical assessment alone. ACEP has established their evidence in adult PSA as a Level A recommendation for the use of propofol, Level B for etomidate and the combination of propofol and ketamine, and Level C for the use of ketamine alone. Brief-acting sedative agents confer shorter periods of impaired levels of consciousness (21-30) benefit of shorter periods of patient impaired consciousness is a reduction in patient monitoring time, which allows reduced allocation of intense patient monitoring periods by medical and nursing staff. We believe that PSA can be performed safely and effectively by EPs in the ED. The majority of AEs experienced by patients in our study were transient, harmless, and successfully solved by the EP. Finally, to encourage cooperation between Italian EDs and the sharing of drug protocols to standardize patients' pathways, we suggest the creation of an Italian SPA registry.

Ethic Committee: The research followed the Declaration of Helsinki ethical principles and the international standards of Good Clinical Practice. The local Ethics Committee approved the protocol (protocol number 2024/0033839).

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: All the authors conceived the study and were responsible for the design of the study. GB conduct of the study and data collection. EF provided statistical advice on study design and analyzed the data. GB, EP and AV drafted the manuscript, and all authors contributed substantially to its revision. GB takes responsibility for the paper as a whole.

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