Procedural sedation and analgesia by Italian emergency physicians: a retrospective observational pilot study

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Abstract

Procedural Sedation and Analgesia (PSA) is a routine practice in Emergency Departments (EDs) but few data exist in the setting of Italian ED. Thus, this study aimed to describe for the first time an Italian experience of PSA in the ED, defining usual indications, types of drug used, efficacy, and safety. We retrospectively collected consecutive adult patients undergoing PSA in the ED of the Santa Croce e Carle Hospital in Cuneo, Italy, over 6 years; we enrolled all patients who received at least one of the four drugs used for PSA (midazolam, propofol, ketamine, and fentanyl). 384 patients (62.2% male; median age 61 [42;76] years) were included in the study. Two hundred and six PSA (53.7%) were done for orthopedic maneuvers, 103 (26%) for electrical cardioversions (ECV), and 75 (19.5%) for other unpleasant medical procedures. A single drug was used in 132 cases (34.3%), while in 252 (65.7%) an association of at least two drugs was used; 239 patients (62.2%) were ASA class I, 144 (37.5%) were ASA class II and one patient was ASA class III. Three patients (0.8%) experienced PSA failure. Minor adverse events occurred during 16 procedures (4%), while no major adverse events, rescue intubation, or need for escalation of care were registered. PSA is currently used in Italian EDs and it is safe when performed by EPs for patients in ASA class I and II. An Italian prospective PSA register is to be created.

Introduction

Pain prevalence in the Emergency Departments (EDs) worldwide is high and painful procedures are commonly performed in the EDs.[1,2] Procedural sedation and analgesia (PSA) is a critically important component of comprehensive emergency care and it is an essential technique for Emergency Physicians (EPs). The administration of sedatives or dissociative agents, with or without analgesics, induces an altered state of consciousness while preserving cardiorespiratory function, oxygenation, and airway control. This relieves patients' anxiety, helps them tolerate unpleasant procedures, and facilitates cooperation during potentially painful procedures.[3,4] PSA decreases the length of time necessary to perform a procedure, increases the likelihood of success, and reduces the risk of injury to the patient or health care worker due to uncontrolled movements.[5]

Multiple studies have shown that PSA is safe when it is done in concordance with current guidelines and that it can be safely and effectively performed by non-anaesthesiologist physicians, both in the care of adult and pediatric emergency populations.[4-10] Despite increasing use in recent years, few complete published data exist about the national experience with PSA performed by EPs. This study described for the first time the local experience of an Italian

ED, tracking a record of the efficacy and safety of this procedure in the hands of EPs.[10]

Materials and Methods

We performed a single-center retrospective cohort study using the local procedural sedation registry. Data were collected for all patients undergoing PSA during the period between January 2015 and December 2020, in the ED of Santa Croce e Carle Hospital, a teaching hospital in Cuneo, north-west Italy.

Population

Among the total number of patients registered in the informatic database of our ED over the 8 years (about 77.000/year), we selected all patients who received at least one of the main four drugs used for PSA: midazolam, propofol, ketamine, fentanyl. We also recorded the use of morphine and ketorolac in this contest. Pregnant women and patients younger than 18 years were excluded. By manual check of medical records, we also excluded patients for whom these drugs had been used solely for analgesic reasons, to treat agitation or psychosis, or to prepare airway intubation. A few records contained incomplete data and were also excluded. The fasting state was not an exclusion criterion.[10] For the remaining group of patients undergoing PSA, we analyzed the type of procedure performed, the type, dose, and combination of sedatives and analgesics used, the procedural success rate, the adverse events, and the need for rescue interventions.

The physical status of the study population was defined before PSA, following the American Society of Anesthesiologists (ASA) physical status classification system (Table 1).[10,11]

PSA protocol

Data of every PSA were registered into a local procedural sedation form. All procedures were performed by EPs alone; the teams included at least one ED nurse and one EP with expertise in PSA conduction, airway management, and cardiovascular and airway management techniques, as required by the American College of Emergency Physicians (ACEP).[4] All procedures were performed in a shock room, set up with a monitor and a ventilator, with airway and full resuscitation equipment readily available. In addition, for the management of adverse events, antidotes such as flumazenil and naloxone were available.

A protocol concerning the selection and preparation of patients (such as ASA class and difficult airway assessment), equipment and monitoring requirements, and staff training and competency verification was used for all patients. During the procedure, Blood Pressure (BP), Respiratory Rate (RR), Pulse Oximetry ($SatO_2$), Heart Rate (HR), and ECG track were recorded. The end-tidal CO2 monitoring ($ETCO_2$) was not used since it was only recently introduced in our setting. Depth of sedation and fasting state were not registered in all patients. Every single EP was responsible for pre-procedure assessment, sedation plan, drug choice and dosing, and monitoring of the patient. Monitorization was discontinued when the level of consciousness returned to before sedation, vital signs were stable, and patients had no pain. In all cases, patients were discharged or transferred after a minimum of 2 hours from the procedure.

Definition of adverse effects and PSA failure

Adverse events during PSA were defined, following the classification of the World Society for Intravenous Anaesthesia (SIVA) International Sedation Task Force (ISTF),[10,12,13] as minimal, minor and major (Table 2). A one-sided binomial test (considering an adverse events incidence of 0.01) was used to report the occurrence of adverse events in the study. The need for respiratory support with a self-expanding balloon during PSA was not considered an adverse event because it is a possible and predictable consequence of deep sedation. Desaturation was hence reported in the adverse events section of our register only when it required mechanical respiratory support or was unexpected or prolonged.

PSA failure was defined as the need to resort to anaesthesiologic assistance for the need to add further sedative drugs or for supportive management.

Analysis

Clinical and procedural data from the PSA paper form were entered into a database. Categorical variables are expressed as numbers (percentages) and continuous ones as median (25^{th} percentile; 75^{th} percentile). Statistical analyses were performed by the JASP software. This study was performed under the Declaration of Helsinki and was approved by the local ethics committee.

Results

384 potentially painful procedures were performed using PSA in our ED. The median age of patients undergoing PSA was 61 [42;76] years and 239 patients (62.2%) were male. All patients were in a low or medium ASA risk class and most of them were in ASA class I (Table 3). The majority of procedures requiring PSA were orthopedic (206, 53.7%), mainly fractures and dislocation

Table 1. American Society of Anesthesiologists classification, adapted from American Society of Anesthesiologists.

ASA I	A normal healthy patient. *Example: Fit, BMI under 30, nonsmoking.*
ASA II	A patient with a mild systemic disease. *Example: Patient with no functional limitations and a well-controlled disease (e.g., treated hypertension, obesity with BMI under 35, frequent social drinker or is a cigarette smoker).*
ASA III	A patient with a severe systemic disease that is not life-threatening. *Example: Patient with some functional limitation as a result of disease (e.g., poorly treated hypertension or diabetes, morbid obesity, chronic renal failure, a bronchospastic disease with intermittent exacerbation, stable angina, implanted pacemaker).*
ASA IV	A patient with a severe systemic disease that is a constant threat to life. *Example: Patient with functional limitation from severe, life-threatening disease (e.g., unstable angina, poorly controlled COPD, symptomatic CHF, recent (less than three months ago) myocardial infarction or stroke.*
ASA V	A moribund patient who is not expected to survive without the operation. The patient is not expected to survive beyond the next 24 hours without surgery. *Examples: ruptured abdominal aortic aneurysm, massive trauma, and extensive intracranial hemorrhage with mass effect.*
ASA VI	A brain-dead patient whose organs are being removed with the intention of transplanting them into another patient

reductions, followed by Electrical Cardioversions (ECV; 103, 26.8%). The remaining procedures were 75 (19.5%) and have been grouped under the name 'other procedures': these included abscess drainage, radiological examinations, and painful medical procedures like thoracic drainages or wound medication. The number of procedures carried out each year gradually increased over the years (47 in 2015, 36 in 2016, 29 in 2017, 59 in 2018, 107 in 2019, and 106 in 2020), with a substantial overlap in the percentage of indications.

Data about drugs used for PSA are reported in Table 4. For 132 patients (34.3%) PSA was performed using a unique drug, mostly midazolam (83 patients, 21.6%), followed by fentanyl (36 patients, 9.4%), and propofol (13 patients, 3.4%). In most patients (252, 65.7%) two or more drugs were associated, with different combinations. The preferred drug association was midazolam + fentanyl (186 patients, 48.4%).

Midazolam as a monotherapy was mostly used for other procedures (67% of cases), but also for orthopedic procedures (19,5% of cases) and ECV (13,5% of cases). The dose of midazolam decreased progressively during the study period (from 10 mg per patient in 2015 to 4 mg in 2020), while its use as a unique drug for PSA increased, contrarily to the use of propofol and fentanyl alone, which decreased through the years. Propofol alone was used in 53% of cases for ECV and in 47% of cases for orthopedic procedures. Fentanyl as a monotherapy was mostly used for orthopedic (67% of cases) and other procedures (31% of cases).

The association midazolam + fentanyl was used in patients with a median age of 57 years old and mostly for orthopedic procedures (73% of cases), while its use was less frequent for ECV (25% of cases) and other procedures (2% of cases). The utilization of this combination of drugs progressively increased through the study years, passing from 21.7% of total procedures in 2015 to 52.3% of total procedures in 2020. The average dose used for each procedure was 8,1 mg of midazolam and 71 mcg of fentanyl.

The median age of patients who received the association propofol + fentanyl was 61 years, and this combination of drugs was used for orthopedic maneuvers in 58% of cases, for ECV in 37% of cases, and for other procedures in 5% of cases. The average dose used was 83 mg of propofol + 62 mcg of fentanyl. During the study period, the prevalence of use of this drug combination remained stable, as well as the average dose used.

The global average dose of midazolam was 8 mg/patient, of fentanyl was 72 micrograms/patient, of propofol was 81 mg/patient. Not enough data were available about the use of Ketamine since it was introduced for PSA in our ED just in the last months of the studied period.

PSA failure occurred in 3 cases (1%). No major adverse events occurred in this study. 16 patients (4,2% of the total population, p = 1) experienced minor adverse events due to PSA: in 8 cases (50%) a short period (< 60 seconds) of desaturation was registered, with oxygen saturation always > 75%, in 7 cases (44%) hypotension was registered and in 1 case (6%) psychomotor agitation

Table 2. Adverse events, adapted from the World Society for Intravenous Anesthesia International Sedation Task Force classification.

	Description	Interventions	Outcome
Minimal	- Vomiting / Retching - Subclinical respiratory depression - Muscle rigidity, myoclonus - Hypersalivation - Paradoxical response - Recovery agitation - Prolonged recovery	- No intervention Performed - Administration of: o Additional sedative(s) o Antiemetic o Antihistamine	No adverse outcome
Minor	- Oxygen desaturation (75–90%) for <60s - Apnoea, not prolonged - Airway obstruction - Failed sedation - Allergic reaction without anaphylaxis - Bradycardia - Tachycardia - Hypotension - Hypertension - Seizure	Airway repositioning Tactile stimulation or the administration of supplemental oxygen, new or increased; antisialogogue	
Moderate		- Bag valve mask-assisted ventilation - Laryngeal mask airway - Oral/nasal airway - CPAP - or the administration of: o Reversal agents o Rapid i.v. fluids o Anticonvulsant i.v.	Unplanned hospitalization or escalation of care
Sentinel	- Oxygen desaturation, severe (<75% at any time) or prolonged (<90% for >60 s) - Apnoea, prolonged (>60 s) - Cardiovascular collapse/ shock - Cardiac arrest/absent pulse	- Chest compressions - Tracheal intubation or the administration of: - Neuromuscular block - Pressor /epinephrine - Atropine to treat bradycardia	-Death -Permanent neurological deficit -Pulmonary aspiration syndrome

CPAP, Continuous Positive Airway Pressure.

occurred. The median age of these patients was 67 years; in 56% (n=9) of cases, adverse events occurred during ECV (8,7 % of all ECV), in 31,2% (n=5) during orthopaedical procedures (2,4% of all orthopaedical procedures) and 12,5% (n=2) of cases during other procedures (2,6% of all other procedures). 12 patients (75%) who experienced minor adverse events were ASA class II and 4 patients (25%) were ASA class I. Most of these patients (10 patients, 62,5%) had received drug associations (Table 5).

Compared to the entire cohort, patients who underwent an adverse event significantly differed for ASA class (75% of the patients with adverse events were classified as ASA II, compared to 37.5% in the whole cohort, $p<0.05$), and for indication (more often ECV; 56.3% vs 26.8%, $p<0.05$).

Discussion

PSA is an essential component of the European Core Curriculum for Emergency Medicine proposed for the first time by EUSEM (European Society of Emergency Medicine) in 2002 and subsequently revised in 2017 and 2019 and is considered a core skill for EPs worldwide.[3,4,10] Italian emergency medicine-trained physicians have the skills for airway management and ventilation, resuscitation, critical care, monitoring, and pain management[3] but they rarely have a well-established track record of safe sedation. This might be one of the reasons why in Italy few and incomplete published data exist about the national experience in this setting, but there are other possible reasons. Firstly, the Italian training program for Emergency Medicine is relatively new, which could mean that research is still in its infancy.[6] Secondly, there is incomplete support from the Italian Drugs Agency (AIFA) regarding the use of certain drugs by EPs.[14] There are also concerns about excessive sedation,[15] and some doctors may continue to favor short procedures performed in the operating room under general anesthesia, or in the emergency department without adequate analgesia or sedation.[5] To address these issues, we have set out to create the first Italian record of PSA indications, policy, and safety. This study demonstrates that the use of PSA significantly increased in our ED during the studied period, as a likely consequence of the increasing expertise of EPs in managing patients who need PSA. During the last few years, the use of PSA has not only increased for orthopedic procedures or ECV but also for common painful procedures such as radiological examinations or abscess drainage. A continuous growth of this technique is expected in the future years, thanks to the increase of PSA experience among the Italian EPs, leading to better confidence in handling sedative-hypnotic drugs and managing side effects. Italian EPs must receive increasingly greater training on PSA, which must be part of the training curriculum; furthermore, these skills must be tested periodically with specific refresher sessions.

Through time, thanks to the increasing experience in PSA, the average dose of many drugs had a descending trend. In most cases, polypharmacy was preferred. The association midazolam + fentanyl was the most used association in our study and was mostly preferred for orthopedic procedures. EPs may have chosen to administer a combination of these drugs due to the availability of their respective antidotes. In case of side effects, especially in older patients, the rapid reversal of midazolam's effect can be achieved with flumazenil, while the effect of fentanyl can be quickly reversed with naloxone. This could have been a reassuring factor for the physicians. The lower use of propofol compared to midazolam in our study, both as a monotherapy or in association with fentanyl, differs from what is described in the literature, which reports propofol alone or associated with other analgesics as the most commonly administered medication for PSA.[18,19] One of the reasons for this choice could be the increased use of PSA for abscesses drainage, painful medical procedures (e.g. wound medication) or to facilitate radiological examinations. These procedures require longer sedation time than ECV and orthopedic maneuvers and may be better covered by the longer half-life of midazolam.[4,20] Another reason is AIFA's regulatory incomplete support for the use of propofol by non-anaesthesiologists. In any case, no restrictions are

Table 3. Patients baseline characteristics.

Characteristics of patients n = 384 (%)	
Age (years)	61 [42;76]
Male	239 (62.2)
ASA class I	239 (62.2)
ASA class II	144 (37.5)
ASA class III	1 (0.3)
PSA indication	
Orthopaedical procedures	206 (53.7)
Electrical cardioversion	103 (26.8)
Other procedures	75 (19.5)
Adverse events	16 (4)
PSA Failings	3 (0.8)

Table 4. Patients baseline characteristics.

Used drug(s)	N (%)
Midazolam alone	83 (21.6)
Fentanyl alone	36 (9.4)
Propofol alone	13 (3.4)
Fentanyl + midazolam	186 (48.4)
Fentanyl + propofol	44 (11.5)
Fentanyl + midazolam + propofol	12 (3.1)
Other combinations	10 (2.6)
Total monotherapy	132 (34.3)
Total polytherapy	252 (65.7)

Table 5. Adverse events.

Patients with adverse event characteristics n = 16 (%	
Age	67 [49;77]
Adverse events	
Desaturation	8 (50)
Hypotension	7 (44)
Psychomotor agitation	1 (6)
ASA I	4 (25)
ASA II	12 (75)
PSA indication	
Orthopaedical procedures	5 (31.2)
Electrical cardioversion	9 (56.3)
Other procedures	2 (12.5)
Monotherapy	6 (37.5)
Polytherapy	10 (62.5)

ASA, American Society of Anesthesiologists Classification, PSA, Procedural Sedation and Analgesia.

given about this choice, since studies reporting the use of either midazolam and/or propofol for PSA in the EDs resulted in no significant difference in safety profile and proportion of successful procedures between agents.[21] Of note, in previous studies, propofol required less monitoring and had lower costs than midazolam.[22] Not enough data were available about ketamine and ketofol use in this study, due to the late introduction of ketamine for PSA in our ED. Ketamine safety and clinical and procedural advantages over other drugs[4,20,23-26] will probably lead to a growth of its use in the next years, which might result in a lower utilization of the other sedatives and analgesics.[24-26] It should be noted that also the combination of ketamine and propofol (so-called ketofol) is gaining ground as an effective and safe option for PSA.[27] The use of the two drugs allows reducing the doses of each, minimizing potential adverse effects. The use of ketofol has demonstrated a lower incidence of respiratory depression than propofol alone; furthermore, the recovery time seems to be significantly shorter.[28,29]

As previously described, the frequency of adverse events, mainly desaturation and hypotension,[30] is low in our study. The median age of patients who experienced adverse events during PSA does not differ from the average age of the total population, as documented also in other studies.[19] The majority of adverse events were registered during ECVs. As seen in another study, the prevalence of adverse events increases with the ASA class:[19] in our study, the majority of adverse events (75%) occurred in patients with ASA class II while only 4 patients (25%) in ASA class I experienced an adverse event.

A slightly greater number of minor adverse events were reported in patients who received drug combinations, particularly midazolam + fentanyl, compared to single-drug therapy. It is known that drugs in combination differ in times of onset and peak effect so that the effect can be less predictable or difficult to titrate.[31] However, the synergic effect of drug combinations, when appropriately dosed, may allow the administration of lower doses of the single drugs.

Due to the small number of adverse events in the total study population, it cannot be determined whether one drug or combination of drugs is associated with a higher rate of minor adverse events than the other. Additionally, it is common for various sedatives and analgesics used for PSA to cause minor adverse events, which are non-specific.[19]

Hypoxia is by far the most frequent adverse event described during PSA,[4] however, not all studies exclude respiratory support from adverse events as we did, which leads to a difficult comparison.[4] A useful way to further reduce the incidence of hypoxia and desaturation would be the use of capnography,[4] which we plan to implement in our clinical practice.

In our study, no major adverse events were registered, in line with the very small proportion found in other studies.[6,21,30-32] This data and the 99% PSA success rate resulting in our study, support the international evidence on the safety and efficacy of PSA performed by adequately trained EPs in the ED.[6,9,21,31,32]

This study has limitations. Firstly, it was a retrospective, single-centre study, aiming to describe the current situation in our ED and to produce preliminary data to be confirmed in larger, prospective, multicentre studies. Secondly, data were obtained from medical records compiled during ordinary ED activity, which could therefore be incomplete. In addition, the body weight of patients was often unreported, making it impossible to calculate the amount of drugs administered per kg. We were not able to collect vomiting and nausea as adverse events. Furthermore, considering that this is a retrospective study over 8 years, we acknowledge that the casuistry is low; this is probably due to the delay with which Italian EPs gained experience in PSA. Lastly, the absence of a standardized procedure for drugs and dosages is another limitation of the study.

Despite nowadays PSA is usually performed by EPs in Italian EDs, official national guidelines have not yet been established. In 2019, a multicentre interregional prospective study named SEED (Sedation in Emergency Department) was started and is currently ongoing; this study aimed to define a national operating standard that encourages, supports, and regulates PSA performed by EPs in the Italian EDs.

Conclusions

PSA appeared to be an effective and safe procedure when performed by EPs with adequate resuscitation and respiratory support skills, with a high success rate and low incidence of adverse events for patients classified as ASA I-II. In this study, PSA was mostly performed using drug associations, in particular midazolam + fentanyl. Larger prospective national studies are needed to define a national operating standard that encourages, supports, and regulates EPs performed by PSA in the Italian EDs.

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