



# Challenges in procedural sedation and analgesia in the emergency department

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**Abstract:** Procedural sedation and analgesia (PSA) constitute a common practice aiming to relieve patients' anxiety, discomfort and pain during invasive diagnostic and therapeutic procedures in the emergency department (ED). The PSA has increased recognition by different specialties, such as Emergency Medicine, Pediatrics, Dentistry, Gastroenterology, Orthopedic, and General Surgery. However, PSA is usually used in orthopedic interventions, abscess incisions, and cardioversion. Desirably, the ideal agent for PSA in the ED should provide anxiolysis, analgesia and amnesia in a rapid, predictable manner, with minimal side effects, and should have a quick recovery phase. Today, there is significant variation in PSA administration, based on individual institutional parameters and physician preferences despite the extensive efforts of several organizations and medical societies to provide universal evidence-based guidelines. Also, a variety of logistic and practical difficulties, such as drug availability and appropriate personnel training, prevent the implementation of global guidelines regarding PSA in the ED. Nevertheless, the proper drug and management strategy has yet to be defined. In the present review, we discuss the assessment and monitoring necessary for PSA administration, the most commonly available and used pharmaceutical agents and the required knowledge, skills, and interventions that are necessary to manage potential complications related to PSA in the ED setting.

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## Introduction

Procedural sedation and analgesia (PSA) constitutes a rather common practice aiming to relieve patients' anxiety, discomfort and pain during invasive diagnostic and therapeutic procedures or diagnostic imaging (1). PSA aims to suppress the patients' level of consciousness while maintaining purposeful response to verbal commands, a state

known as moderate sedation (2). The emergency department (ED), along with the intensive care unit (ICU), are the two most common settings of PSA administration (3).

PSA administration in the ED has been gaining attention amongst the medical community as it concerns various specialties, namely Emergency Medicine, Anesthesiology, Pediatrics, Orthopedic Surgery etc. The most common procedures associated with its use include orthopedic

manipulations, abscess incision and drainage, wound debridement and direct current cardioversion (1).

The ideal agent for PSA in the ED should provide anxiolysis, analgesia and amnesia in a rapid, predictable manner, with minimal side effects, and should have a quick recovery phase (1). One of the most important obstacles in the implementation of PSA in the ED is the variability of sedative drugs' availability worldwide (4). This results in the application of local or national guidelines, regulated by the availability of sedative agents and personnel, making the implementation of universal guidelines challenging (1,5).

There is a plethora of controversies regarding PSA in emergency settings, amongst them the appropriate level of sedation, the selection of the proper pharmaceutical agent and the management of potential adverse effects. It is thus essential to manage ED patients using a multidisciplinary team approach and establish standardized protocols for PSA administration. Towards this end, the European Society of Anesthesiology (ESA) and the European Board of Anesthesiology launched guidelines regarding PSA in adults in 2018 (1), that were twice updated since (6,7).

In the present review, we discuss the assessment and monitoring necessary for PSA administration, the most commonly available and used pharmaceutical agents and the required knowledge, skills, and interventions that are necessary to manage potential complications related to PSA in the ED setting.

## Assessment and monitoring for PSA

### *Pre-sedation assessment*

In the ED, pre-sedation assessment is usually challenging due to specific, setting-related parameters, such as urgently-needed anesthesia for patients with potentially severe comorbidities. Whenever feasible, a pre-sedation assessment should be conducted, including a focused history and physical examination and a review of comorbidities, medications and allergies (8). The most widely used scheme is the American Society of Anesthesiologists (ASA) Physical Status Classification, aiming to identify patients at risk of adverse events (9).

### *Pre-procedural fasting*

The depression of upper-airway reflexes during anesthesia is a major risk factor for the development of aspiration pneumonia (10). Thus, ASA recommends pre-procedural

fasting before the administration of sedation (11). However, it is easily understandable that pre-procedural fasting cannot be considered routinely applicable in the ED. Fortunately, the moderate sedation achieved during PSA administration in the ED does not suppress protective airway reflexes (10). Moreover, no deaths from aspiration have been reported in the literature associated with PSA administration in the ED (12). Consequently, the American College of Emergency Physicians (ACEP) does not consider recent food intake as a contraindication for PSA in the ED (2).

### *Monitoring equipment*

In line with ACEP guidelines, it is standard practice to continuously monitor the patient's cardiac rhythm (electrocardiogram), pulse rate, oxygen saturation, and respiratory rate during PSA in the ED (2). Blood pressure is typically measured in a non-invasive manner every five minutes (13). In addition to the above, suction devices, supplemental oxygen and advanced monitoring equipment should be readily available (2). Finally, advanced airway equipment, resuscitative medications and vascular access supplies should be easily accessible (2). Moreover, core body temperature monitoring is recommended by ASA in patients who receive moderate or deep sedation, unless restricted by the patient's status, the available equipment or the procedure itself (14).

Capnography (end-tidal carbon dioxide monitoring) is used for the detection of early signs of respiratory depression (15,16), however its routine use for PSA in the ED is debatable. In a meta-analysis conducted in 2011, Waugh *et al.* (17) reported an increased rate of detection of respiratory depression (17.6 times higher) when comparing capnography with standard monitoring alone. On the other hand, it has been suggested that the detection of apnea or transiently decreased ventilation by capnography could lead to unnecessary interventions, like positive pressure ventilation and may result in complications such as aspiration and gastric insufflation (15). Additionally, capnography implementation has not been proven effective in foreseeing desaturation episodes or in decreasing the incidence of clinically important adverse effects (18-23). Therefore, capnography is not considered standard of care for PSA in the ED.

### *Sedation scales, responsiveness monitoring*

Numerous sedation/responsiveness scales are available for

use during PSA, nevertheless none has been proven superior to the other in evaluating sedation efficacy (24). The most frequently cited scales are the Observer's Assessment of Alertness/Sedation Scale, the Richmond Agitation-Sedation Scale and the Ramsay Sedation Scale (25,26). In addition to using established scales to monitor a patient's responsiveness, patients' distress, ventilatory adequacy and procedural recall can be used as indirect measures of PSA effectiveness (27).

### Sedative agents and their adverse effects

A vast amount of sedative drugs are available worldwide, with their accessibility varying amongst different countries. As a result, the establishment of globally applicable guidelines is challenging. A review article published by Gozal and Mason in 2010 (28) addressed this specific topic and although they elaborated on pediatric sedation their conclusions may be applicable on adult populations too. Based on randomized controlled trials (RCTs) and meta-analyses, they propose that traditional sedation agents, like ketamine, midazolam, propofol, etomidate and nitrous oxide should maintain their primary role in PSA. Furthermore, they suggest that some combinations, such as ketamine-midazolam and ketamine-propofol may be beneficial due to their synergistic effect (28). Characteristics of the most commonly used anesthetic agents are shown in *Table 1*.

#### *Propofol*

Propofol is the most commonly used sedative drug because of its fast onset of sedation and predictability of effect duration. Hepatic clearance is high, so accumulation of the drug is negligible even after repeated administrations or continuous infusion. The initial effects of propofol include mild sedation and amnesia, leading to deep sedation when administered in high doses. Doses needed for induction of anesthesia are 1–2.5 mg/kg, whereas plasma concentration needed for sedation is 1–2 mcg/mL (29).

Propofol can be used in a variety of procedures. It has been showcased that it provides patient satisfaction, better quality of sedation and faster recovery in gastrointestinal endoscopy interventions (30). Therefore, a new position statement from the British Society for Gastroenterology and the Royal College of Anesthetists proposes propofol administration for the execution of complex gastrointestinal endoscopies (31). Moreover, in a study by Mathieu *et al.* in 2009 (32), a sedation regimen using propofol was more

successful than the previously preferable midazolam/analgesic combination in achieving optimal conditions for dislocated hip prosthesis reductions.

Target Control Infusion (TCI) pumps allow for more precise control over the level of sedation, although there is a shortage of data concerning the use of TCI in the ED (33). A RCT, termed "The Propofol Target-Controlled Infusion in Emergency Department Procedural Sedation" (PROTEDS) is underway, aiming to assess the safety and efficacy of TCI-administered propofol, as well as the practicalities of its use in the ED for dislocated shoulder reduction (34). A similar idea, called "The Computer Assisted Propofol Sedation System" (CAPS), was implemented as a substitute of the bolus propofol injection by anesthesiologists, but due to high cost and low profitability the project was discontinued by the manufacturer. However, the experience of hospitals where CAPS was used was positive (35).

Propofol administration in the ED may result in various adverse effects, such as apnea, hypoxia, and hypotension (36). Therefore, the presence of personnel qualified in airway management and resuscitation is essential. Homfray *et al.* assessed the adverse effects of propofol, midazolam/morphine and other sedative agents in a population of 704 elderly patients in their safety analysis in 2018. The overall sentinel adverse effect rate (hypoxia, apnea, hypotension) was 2.6%, but no safe conclusions could be drawn when comparing propofol with other agents. It is interesting to note that in this particular population, a bolus propofol dose of 0.5 mg/kg with a subsequent bolus dose of 0.25 mg/kg, if sedation was unsatisfactory, resulted in the lowest rate of adverse effects. However, the overall rate of adverse events noted during propofol administration was high, accentuating the need for further research in sedation practices (37).

#### *Midazolam*

Midazolam is a fast-acting benzodiazepine with a short half-life (38). It has anxiolytic, sedative and anterograde amnesic effects in lower doses, while deep sedation is achieved when administered in higher doses (39). It has no proven analgesic properties, however there are limited indications that intravenous administration of midazolam prior to nasogastric tube insertion leads to reduced self-reported pain (40). Midazolam is the pharmaceutical agent most commonly used for PSA in the ED in the United Kingdom (41). The recommended dosing range is 0.1–0.3 mg/kg in

**Table 1** Characteristics of the most commonly used anesthetic agents

Drug name (drug class)	Mechanism of action	Clinical applications	Administration route	Dosage	Pharmacokinetics	Adverse effects
Midazolam (Benzodiazepines)	• GABA <sub>A</sub> receptor binding → increases the frequency of chloride channels opening	• Preoperative sedation	IM	0.1–0.3 mg/kg	• Hepatic metabolism	CVS: CVS depression, hypotension, bradycardia
		• Preoperative amnesia	IV		• Half-life: 2–4 hrs	• Respiratory: hypoxia, apnea
		• Epilepsy • Anxiolysis	Intranasal			• GIT: vomiting
Propofol (General Anesthetics)	• Decrease GABA dissociation from its receptor → increases the duration of chloride channel opening	• Sedation • Anesthesia Sedation • Anesthesia	IV	1–2.5 mg/kg	• Hepatic metabolism • Half-life: 40 mins (initial), 24–72 hrs (after 10-day infusion)	CVS: hypotension • Respiratory: respiratory depression, hypoxia, apnea
Ketamine (General Anesthetics)	• NMDA receptor antagonist	• Analgesia	IM	Analgesia: 1–2 mg/kg Sedation: 3–9 mg/kg	• Hepatic metabolism	• Musculoskeletal: myoclonus, laryngospasm
		• Sedation	IV		• Half-life: 3 hrs	• GIT: vomiting
		• Anesthesia	Intranasal			• Other: recovery agitation, hypersalivation
Etomidate (General Anesthetics)	• GABA <sub>A</sub> receptor binding → increase affinity of GABA for its receptor → potentiation of chloride currents	• Sedation • Anesthesia	IV	0.1–0.5 mg/kg	• Hepatic metabolism • Half-life: 75 mins	CVS: hypotension, arrhythmia • Respiratory: apnea, hypoventilation • Musculoskeletal: myoclonus • Other: transient injection site pain
Fentanyl, Morphine (Opioid analgesics)	• Strong $\mu$ agonists • Variable $\kappa$ and $\delta$ effects	Analgesia	IM	Fentanyl: 1.0–5.0 mcg/kg	• Hepatic metabolism	CVS: bradycardia
		• Sedation • Anesthesia	IV	Morphine: 0.1 mg/kg	• Half-life: 2–4 hrs	• Respiratory: respiratory depression • GIT: nausea, vomiting, constipation • Other: cough suppression, pruritus
Dexmedetomidine (a <sub>2</sub> -receptor agonist/sedative)	• Selective a <sub>2</sub> -receptor agonist	• Sedation	IV	1–2 mcg/kg	• Hepatic metabolism	• CVS: heart block, severe bradycardia, asystole, hypotension, pulmonary edema
			Intranasal		Half-life: 4 mins (10 mins infusion)	• Other: anemia

IM, intramuscular; IV, intravenous; CVS, cardiovascular system; GIT, gastrointestinal tract.

divided doses of 1–2 mg until the desired level of sedation is achieved. Midazolam has an immediate onset of effect, a half-life of 2–4 hours and its effects last for roughly 20 minutes (42).

Midazolam in the ED can be administered through the intravenous or intranasal route. Intravenous administration enables precise dosing and faster onset of action, with easy titration of the divided doses. Intranasal application is gaining attention in the pediatric population, as well as in combative patients, while also being a viable option in patients with difficult venous access. Intranasal delivery of the drug is achieved with devices known as “atomizers”. The volume of midazolam administered per nostril should ideally be between 0.2–0.5 mL/kg, with the maximum dose being 1 mL/kg. Since high volumes of drug administration cannot be achieved through the intranasal route, its use is restricted to patients weighing less than 50 kg (43).

The most common adverse effects of midazolam include hypotension, hypoxia and apnea with the incidence estimated at 6.1, 51.2 and 51.4 per 1,000 patients, respectively. Vomiting is a less frequent side effect. Cardiovascular depression, presenting as hypotension or bradycardia, is rare when midazolam is given as a sole agent (44). In case of life-threatening adverse events, a selective GABA<sub>A</sub> antagonist called flumazenil should be administered. It is usually given intravenously or intranasally, in doses of 8.0–15.0 mcg/kg. Its onset of action is fast, but its effect duration brief, rendering re-sedation possible in 20 minutes (45).

### ***Ketamine***

Ketamine is a phencyclidine derivative that causes a dissociative anesthetic state which differs from “classic” sedation. It is a NMDA receptor antagonist with strong analgesic effects (46) that can be used as a first line agent for the management of agitated patients as it acts faster than benzodiazepines and haloperidol (40). In a study by Riddell *et al.*, ketamine displayed a favorable hemodynamic profile, as no significant changes in blood pressure or pulse rate were documented. The administered dosage was 4–5 mg/kg IM with an onset of action at 5 minutes, or an IV dose of 1–2 mg/kg. This single center study was conducted in a population exhibiting a high percentage of methamphetamine abuse, thus presenting a severe limitation in generalizing its conclusions (47).

Ketamine can be used as a sole agent during arduous procedures, such as orthopedic manipulations. In a cohort study by Newton *et al.*, including 92 ED patients, ketamine

provided optimal analgesia and sedation in the majority of the patients. Initial dose was 0.5 mg/kg, repeated after 5 minutes, if sedation was deemed inadequate by the treating physician, to a maximum of 1 mg/kg (48).

In addition to intravenously and intramuscularly, ketamine can also be administered intranasally. The recommended doses are 3–9 mg/kg for sedation and 1–2 mg/kg for analgesia. Maximal concentration of ketamine is 50 mg/mL, limiting the total dose in adults to 100–200 mg. For that reason, intranasal administration of ketamine in this patient population is reserved for analgesic purposes (49).

The unique properties of ketamine allow for preservation of spontaneous ventilation and hemodynamic stability. Its administration can be invaluable in resource-poor settings, where ideal monitoring of respiratory and cardiovascular functions cannot be achieved. Ketamine was well tolerated and deemed satisfactory by patients and physicians alike in a study of 54 children and 54 adults treated for burns and orthopedic injuries in a tertiary hospital in Tanzania (50).

A crucial drawback of ketamine administration is its numerous adverse effects. Those include emergence reactions, such as agitation during recovery from anesthesia, hypersalivation, clonic movements, laryngospasm and vomiting. The most recurrent amongst them is recovery agitation which can be minimized or prevented by the administration of benzodiazepines (49,51).

### ***Ketofol***

“Ketofol” is a ketamine and propofol mixture, which gained popularity because of the theoretical advantages of adding the analgesic properties of ketamine to the hypnotic properties of propofol. Propofol also seems to have the ability to counteract some of the most important ketamine adverse effects; emergence phenomena, nausea and vomiting. Moreover, the addition of ketamine results in reduced dose of propofol needed during PSA, decreasing the possibility for respiratory depression. The recommended dosage is 0.5 mg/kg of a 1:1 mixture, followed by another dose of 0.5 mg/kg. A dose of 0.25 mg/kg is used afterwards for maintenance of sedation (52).

Two recent meta-analyses studied the safety and efficacy of ketofol in comparison with propofol as a single agent. The study by Yan *et al.*, which included six RCTs, concluded that there was no statistically significant difference in safety between the two pharmaceutical agents. While the overall danger of developing adverse events during PSA was not reduced, less respiratory events were documented in the

ketofol group compared with the propofol group. However, the authors emphasize the fact that their meta-analysis included a heterogenous population (adults and children) and a variety of ketamine/propofol ratios were used in their included studies (53). Jalili *et al.* in 2016, attempted to overcome the aforementioned limitation, by only analyzing studies conducted in adult populations. Even so, they reached the same conclusion; ketofol appears to be a safe alternative to propofol for PSA (36).

Ketofol was also compared to a combination of propofol and fentanyl in a cohort study of 136 trauma patients in a university hospital in Iran. The administered doses were 1 mcg/kg of fentanyl, 1.0 mg/kg of ketamine and 0.5 mg/kg of propofol. There were more apneic and hypoxemic events in the group which received the propofol/fentanyl mixture. The authors concluded that the propofol/fentanyl combination can be recommended over ketofol because of its superior sedation quality and analgesic effects (54).

The combination of ketamine and propofol appears to be safe in patients with cardiogenic shock, due to the lesser influence of ketamine on hemodynamic parameters (46). A new PPIIM protocol (Preoxygenation, Pretreatment, Induction of anesthesia and paralysis, Intubation, Mechanical ventilation) was evaluated by Chalkias *et al.* in 2018, including 31 patients suffering from acute myocardial infarction and presenting signs of cardiogenic shock. They compared those patients to a historical control group, matched by patient characteristics, that received standard RSI (rapid sequence induction) with either midazolam, propofol or etomidate. The protocol included the use of fentanyl as pretreatment (0.7 mcg/kg) and midazolam (0.02 mg/mg), ketamine (0.35 mg/mg) and propofol (0.5 mg/kg) for the induction of anesthesia. They concluded that the patients who received the ketamine/propofol (ketofol) combination had improved hemodynamic parameters (systolic, diastolic and mean arterial pressure) and a higher rate of survival in comparison with the control group (55).

### *Dexmedetomidine*

Dexmedetomidine is a highly selective  $\alpha_2$  receptor agonist. The effects of central  $\alpha_2$  receptor potentiation include anxiolysis and sedation, without concurrent respiratory depression. Its half-time is only 4 minutes when administered in 10-minute infusions but can be prolonged through longer administration (56).

A study in patients with anterior shoulder dislocation showcased better analgesic effects and faster recovery

with dexmedetomidine administration when compared with a midazolam-fentanyl combination (57). Recently, dexmedetomidine was confirmed to be safe for use in upper gastrointestinal endoscopy (58). Intranasal administration of dexmedetomidine is possible, with the proposed dosage being 1–2 mcg/kg. The onset of sedation for adults is reported to be 45 minutes, with a 90–105 minutes interval for achieving peak sedation (59).

Adverse events include heart block, severe bradycardia and asystole, due to unopposed vagal stimulation. There are minimal changes in ventilatory rate and tidal volume (56).

### *Etomidate*

Etomidate is a sedative-hypnotic drug that potentiates the activity of GABA<sub>A</sub> receptors. It has minimal effects on cardiovascular function, but suppresses cortisol production for 4–8 hours, a factor that limits its use in continuous infusions (60). There are limited new studies addressing the use of etomidate in PSA.

In advanced endoscopic procedures etomidate has been shown to be as efficacious as propofol in achieving sedation with less cardiopulmonary adverse effects (61). Furthermore, ventilation depression is less pronounced compared with propofol, but episodes of apnea may occasionally occur. Its effects on the cardiovascular system are minimal, although caution is advised when etomidate is used in hypovolemic patients as it can lower blood pressure significantly (42). In a RCT by Miner *et al.*, propofol was found to be more efficient than etomidate with similar adverse event rates, except for myoclonus rate which was significantly higher in the etomidate group (20% versus 1.2%). It was hypothesized that the lower success rates of etomidate were related to myoclonus events (62).

In a study for the treatment of various pediatric orthopedic injuries, etomidate combined with fentanyl showed similar sedation levels to ketamine but required administration of multiple doses because of its short duration of action. The authors concluded that they would prefer ketamine to etomidate since it provides longer sedation time (63). In another study in an adult population with large joint dislocations, no difference was found in the conditions of reduction when etomidate, in doses of 0.1 or 0.5 mg/kg until adequate sedation was achieved, was compared to ketamine. However, patients in the ketamine group experienced fewer desaturation episodes and interventions to maintain airway patency were less frequently needed (64).

## Opioids

Opioid drugs act on opioid receptors throughout the central nervous system, providing an analgesic effect, as well as hypnotic and sedative effects in high doses. They are mostly used as adjuncts to sedatives that do not possess analgesic effects. The most commonly used opioids for sedation and analgesia are fentanyl and morphine.

The usual dose of opioids is 1.0–5.0 mcg/kg and 0.1 mg/kg for fentanyl and morphine respectively. Fentanyl has a faster onset and shorter duration of action, rendering it easier to titrate than morphine and a sensible choice for PSA. Furthermore, fentanyl has the considerable advantage of being available for intranasal administration in both children and adults. The adverse events associated with opioid administration are numerous, including respiratory depression, cough suppression, nausea and vomiting, bradycardia, constipation and pruritus; most of these adverse effects are dose related. It is important to mention that the addition of fentanyl to midazolam results in a 4-fold increase in unwanted respiratory events in comparison to midazolam administration alone (65).

In case of severe adverse events, a competitive opioid receptor ( $\mu$ ) antagonist called naloxone should be administered, usually through the intravenous or intramuscular route. Its onset of action is 2 minutes and its appropriate dose ranges between 0.4 to 1 mg in adults and 0.1 mg/kg in children. However, patients who have been injected with high doses of fentanyl may subsequently require a higher dose of naloxone administration (66).

## Inhaled anesthetics

Currently, potent inhaled anesthetics are rarely used in the ED, owing to the need for anesthesia machines and trained personnel. However, inhaled agents have gained attention as sedatives in the emergency setting, as they alleviate the need for intravenous access. This fact makes inhaled anesthetics a viable option for sedation, especially in the pediatric population (67).

There are a few case cohort studies regarding the use of sevoflurane after dental trauma in the pediatric ED (68,69). Kim *et al.* presented their experience in managing agitated children with dental trauma using sevoflurane. The inhaled agent was administered through an intranasal cannula and the end-tidal sevoflurane was monitored in order to maintain adequate sedation. No complications were documented and all children maintained spontaneous

ventilation throughout the procedure (69).

Nitrous oxide ( $N_2O$ ) is another inhaled sedative which can be used for PSA in the emergency setting. It is typically administered as a 50–50% or 70–30%  $N_2O$ -oxygen mixture, with at least 30% oxygen to avoid hypoxemia, while a concentration of at least 30% of  $N_2O$  is necessary for adequate sedation. This inhaled agent can be administered by a demand-valve mask or mouthpiece held by the patient (70). Potential adverse effects of nitrous oxide include nausea, vomiting and respiratory depression (71). Brodsky *et al.* (72), advise against nitrous oxide administration in patients with pneumothorax, immunosuppression or possible pregnancy. Self-administration of nitrous oxide by the patient is often preferred in order to avoid over-sedation (73). Sivaramakrishnan *et al.*, concluded that a combination of nitrous oxide and midazolam was preferable to each individual agent alone during PSA. The lower doses of midazolam seemed to improve patient safety and enhance predictability of sedation depth (74).

## Oxygen supplementation

Several publications have shown that the use of general anesthetic and sedative drugs during PSA increases the risk of cardiorespiratory depression and upper respiratory tract obstruction (2,13). Current guidelines highlight the importance of constant monitoring of respiratory function, as well as oxygen supplementation in both moderate and severe sedation in order to prevent any possible adverse effects (2,75). Supplemental oxygen should be provided to all hypoxemic patients unless there are certain contraindications (2,13,75,76). Several RCTs have concluded that hypoxemia rates are markedly reduced following the administration of supplemental oxygen in patients under moderate or severe sedation (13,75).

Although oxygen supplementation during PSA reduces hypoxemia rates, it can obscure the identification of other adverse effects such as hypoventilation and upper respiratory tract obstruction (75). Remarkably, results from studies have demonstrated that regular administration of supplemental oxygen increases the risk of cardiovascular complications (75). The most common respiratory adverse events during PSA are hypoxemia (40.2 per 1,000 sedations) and apnea (12.4 per 1,000 sedations), although they rarely require endotracheal intubation (55). Deitch *et al.* reported that high-flow oxygen supplementation or apneic oxygenation can significantly decrease the incidence of hypoxia during PSA (77).

Even though the beneficial effects of supplemental

oxygen during PSA in the ED have been established, it still remains unclear which route of supplemental oxygen administration is the most beneficial in lowering hypoxemia risk (2).

### *Nasal high flow (NHF) therapy*

NHF therapy is a new oxygen administration method that has been proven to possess many advantages over conventional oxygen treatments (78,79). It was introduced in neonates and infants, but it has been increasingly used in adult populations in recent years (78,80). The oxygen device delivers a combination of heated, humidified air and oxygen at a fraction of inspired oxygen (FiO<sub>2</sub>) ranging from 21% to 100% with a flow rate up to 60 L/min (78,79,81).

Several studies have reported that NHF therapy creates a positive end-expiratory pressure (PEEP) and enhances respiratory function, while improving patients' tolerance. Furthermore, it decreases anatomical dead space and facilitates the function of the mucociliary clearance mechanism (16,78,79).

NHF therapy can be used in patients presenting in the ED with various diseases (79,80). Currently, it is mainly used as the initial treatment in patients presenting with type I and type II acute hypoxemic respiratory failure (80). Further clinical indications include acute heart failure, acute respiratory failure in immunocompromised patients, preoxygenation for intubation and PSA (80). Interestingly, NHF is recommended as the primary method of oxygen supplementation during PSA but no guidelines have been made available regarding its application in clinical practice (78,80).

### *Apneic oxygenation*

Apneic oxygenation is a technique used for airway management in emergency settings (82). Hypoxemia, brain anoxia and cardiovascular collapse consist the main unfavorable outcomes of patients who need urgent airway intubation as a result of a primary pulmonary pathology (82-84). Apneic oxygenation was designed to hinder and reduce the development of such significant adverse non-rebreather events especially during anesthesia induction (83). The results of several published data have shown that the use of apneic oxygenation during tracheal intubation minimizes the risk of arterial oxygen desaturation and extends the interval prior to apnea initiation (84). It is important to emphasize that a patent airway is recommended for the

induction of apneic oxygenation technique (83).

Various techniques are used for the induction of apneic oxygenation including high flow nasal cannula oxygenation, Venturi masks, nasotracheal tubes and face masks. Published data have established the superiority of the high flow nasal cannula method over a non-rebreather facemask in improving arterial oxygen saturation (82).

Apneic oxygenation is not recommended in patients presenting with hyperkalemia, pulmonary hypertension, increased intracranial pressure and metabolic acidosis (84). Finally, it is contraindicated in cases of facial trauma and airway obstruction (83).

### **Rapid sequence induction (RSI)**

RSI of anesthesia is a method used for tracheal intubation in high risk patients (85). The principal elements of RSI include anesthesia induction followed by neuromuscular blocking agents administration and intubation (86). The main goals of the RSI technique are to reach a standard level of anesthesia while simultaneously preventing aspiration by immediate intubation (86). Specifically, it is considered highly important to initiate the intubation within a minute following the administration of anesthesia (86).

Pre-oxygenation is regarded a vital step in the RSI technique, as it has been proven to be beneficial on apnea tolerance (85). The use of ventilation masks has been suggested in cases of obese and critically ill patients in order to avoid the development of hypoxemia throughout the apneic phase (87). The results of various publications have emphasized the significance of this method, particularly for patients with respiratory decompensation, pregnant women and children who have difficulty in tolerating apnea (86).

Application of cricothyroid pressure is considered important in order to reduce the risk of gastric content regurgitation (86). Interestingly, several studies have highlighted the questionable efficacy of applying cricoid pressure (87,88).

The major induction drugs used in RSI method include propofol, etomidate, ketamine and thiopental. Propofol and thiopental are first-line choices whereas ketamine and etomidate are considered alternatives (86). Ketamine is recommended as first line therapy in patients with shock; etomidate is preferred in heart failure patients (86). However, the selection of the induction drug, the proper dosage and the preferred route of administration remain controversial (86).

The administration of sedative agents should be

followed by infusion of a muscle relaxant agent, such as succinylcholine or rocuronium, to facilitate tracheal intubation (86,89). Although succinylcholine had been historically considered the agent of choice, currently it has been substituted by rocuronium (86).

Recently, several alternatives of the RSI method have been introduced, making the establishment of official guidelines challenging, although it is still the preferred method in emergency situations (86,90).

### Resources, quality and training

As previously mentioned, procedural sedation is associated with a number of adverse effects and complications. Therefore, clinicians involved should be adequately skilled in sedation induction, patient monitoring and management of adverse events (76).

Various reporting protocols, aiming to optimize PSA practice, are used in order to record procedural outcomes, adverse effects and physicians' efficacy. The International Committee for the Advancement of Procedural Sedation recommended the use of a new tool for monitoring sedation outcomes in 2018 titled "Tracking and Reporting Outcomes of Procedural Sedation" (TROOPS). TROOPS may be adopted by any interested physician in order to monitor their sedation practices or as a research tool (91).

Respiratory depression and hemodynamic instability are considered the most common and important adverse events of PSA. A meta-analysis including 9,652 PSAs in the ED, reported that apnea, hypotension and bradycardia may occur in 12.4, 15.2 and 6.5 out of 1,000 sedations respectively (44). In rare cases, cardiac arrest may succeed these complications (92). Consequently, PSA providers must be well trained in recognizing and treating life threatening complications that may arise during sedation. That implies that they should be proficient in antidote administration (flumazenil, naloxone), advanced airway management, IV cannulation and cardiac arrest management (Advanced Life Support) (76,93). Finally, physicians should be able to perform pre-procedural equipment checks and accurately assess the patient's medical condition.

ESA recommended the use of a written test as well as a practical course on mannequins to ascertain the sufficiency of trained physicians before their exposure in real-life scenarios (76). Likewise, ASA advises that deep sedation should be restrictedly administered by "qualified anesthesia professionals" or non-anesthesiologist physicians who have been officially trained (94).

The guidelines by ESA also indicate the groups of patients that need to be taken care of by an anesthesiologist, should they undergo PSA, according to their age (>70 years old), their physical status (ASA 3 or 4), or their comorbidities, including severe cardiovascular disease, presence of obstructive sleep apnea, severe renal or hepatic disease and morbid obesity (9).

### Conclusions

In conclusion, a variety of logistic and practical difficulties, such as drug availability and appropriate personnel training, prevent the implementation of global guidelines regarding PSA in the ED. Further multicentric studies with large datasets might contribute in establishing protocols that can be effectively applied in an emergency setting. Non-anesthesiologist physicians' training on sedation should be prioritized in order to administer PSA in a safe and efficient manner.

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