Review

Procedural Sedation in Emergency Department: A Narrative Review

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Procedural Sedation In Emergency Department: A Narrative Review

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Abstract: Procedural Sedation and Analgesia (PSA) in the Emergency Department (ED) presents a crucial aspect of emergency medicine, enabling the execution of painful or distressing procedures with minimal patient discomfort. This narrative review delineates the pharmacological framework, methodologies, and clinical considerations integral to optimizing PSA, with a particular focus on pediatric and geriatric populations. Through a comprehensive review and analysis of current practices, this work evaluates the pharmacokinetics and pharmacodynamics of widely utilized sedatives and analgesics, including propofol, ketamine, dexmedetomidine, fentanyl, midazolam, etomidate, nitrous oxide, and remimazolam. Special attention is dedicated to the selection criteria based on patient-specific risk factors, procedural requirements, and the management of potential adverse effects. The manuscript also explores innovative sedation techniques and the integration of new pharmacological agents, emphasizing evidence-based approaches to enhance patient safety and outcome. Results underscore the significance of tailored sedation strategies, especially for vulnerable groups such as pediatric and geriatric patients, highlighting the need for meticulous pre-procedural assessment and monitoring to mitigate risks. Conclusions drawn advocate for a nuanced application of PSA, guided by current evidence and clinical guidelines, to improve the quality of care in emergency settings. This research reinforces the imperative for ongoing education, skill development, and adaptation of new evidence into clinical practice to advance procedural sedation and analgesia in the ED.

Keywords: procedural sedation; emergency medicine; pharmacological management

1. Introduction

The administration of procedural sedation and analgesia (PSA) in the emergency department (ED) represents a cornerstone of modern emergency medicine, enabling clinicians to perform potentially painful or distressing procedures with minimal patient discomfort and stress, while preserving vital physiological functions [1,2]. This practice necessitates a sophisticated understanding of pharmacology to select and administer sedative and analgesic agents that are best suited to the patient's needs and the specific procedural requirements [3,4].Agents such as propofol, ketamine, dexmedetomidine, fentanyl, midazolam, etomidate, nitrous oxide, and the innovative benzodiazepine remimazolam, each with distinct pharmacokinetic and pharmacodynamic profiles, are judiciously evaluated to ensure their optimal application in procedural sedation [5–12].

Effective PSA in the ED transcends mere pharmacological intervention, requiring a comprehensive patient assessment, strategic planning, and preparation for potential complications. Identifying patient-specific risk factors, including age, existing comorbidities, and physiological reserves, is crucial for customizing sedation strategies that balance efficacy with safety. Such an approach is underscored by clinical guidelines and recommendations that advocate for vigilant monitoring, airway management, and cardiovascular stability throughout the sedation process.

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The unique challenges presented by special populations, such as pediatric and geriatric patients, underscore the necessity for tailored sedation approaches. These groups demand careful consideration due to their specific physiological and pharmacological characteristics, which influence drug metabolism, airway management, and susceptibility to adverse reactions. This manuscript explores these nuanced considerations, proposing evidence-based strategies to enhance care for these vulnerable groups within the ED setting.

Furthermore, the introduction of new sedative agents and advancements in sedation techniques highlight the evolving landscape of PSA. Innovations, exemplified by remimazolam, promise to refine sedation practices with potential benefits in safety and effectiveness [13]. Such developments reinforce the importance of evidence-based practice and patient-centered care, integrating new knowledge into clinical protocols to improve procedural sedation outcomes [14].

In conclusion, PSA in the ED encompasses a comprehensive array of pharmacological options, patient care principles, and clinical techniques. This manuscript aims to provide an in-depth overview of the current state of practice, addressing challenges and highlighting innovations in PSA to foster the delivery of safe, effective, and patient-focused care in emergency medicine. Through detailed discussions on pharmacology, patient assessment, monitoring techniques, and considerations for special populations, this work contributes to the advancement of sedation practices in the emergency setting.

2. Pharmacology in PSA

Procedural sedation and analgesia (PSA) is routinely performed in the emergency department to facilitate potentially painful medical procedures by reducing the patient's discomfort, pain and anxiety. PSA typically involves the intravenous administration of sedative or dissociative agents, with or without the concomitant delivery of analgesics [15]. This strategy enables clinicians to perform procedures effectively and requires monitoring the patient closely for potential adverse effects [16].

The ideal medications for PSA have a rapid onset and short duration of action, with a quick recovery of cognitive and physical faculties, maintain haemodynamic and respiratory stability and have minimal associated risks [17]. To better predict the pharmacokinetic effects, the recommended route of administration is intravenously: most of the drugs used for PSA are injected as single or repeated boluses or as a continuous infusion [18]. Some evidence suggests intranasal administration for drugs such as dexmedetomidine [19].

A combination of drugs is generally required to reach both the hypnotic and analgesic endpoints [20]. The addition of local or regional anesthesia and non-opioid analgesics can help reducing pain levels and the doses of PSA medications needed, as well as decreasing the risk of post-procedural respiratory depression.

There is no clear evidence about which drugs are safer than others; consequently, the type and dose of drug should be chosen and optimized according to both the patient's characteristics and the medications' specific effects and risks [21].

According to the American College of Emergency Physicians Clinical Policies Subcommittee, in patients undergoing PSA in the emergency department, level A recommendation state that Ketamine can be safely administered to children and Propofol can be safely administered to children and adults [15].

2.1. Propofol

Propofol is a short-acting intravenous anesthetic produced in 1975, used as an induction agent for general anesthesia and during monitored anesthesia care. It has also been used for procedural sedation in the emergency department since 1996 [22].

Propofol (2,6-diisopropylphenol) is a derivate of short-acting alkylphenols [23]: it is prepared in a lipid emulsion which gives it a characteristic milky white appearance, containing soybean oil, glycerol, egg lecithin and a small amount of EDTA, the latter to prevent bacterial contamination. A number of different formulations of propofol are currently available.

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Like most anaesthetics, propofol is a γ-aminobutyric acid (GABA) receptor agonist and has a favourable pharmacokinetic (PK) and pharmacodynamic (PD) profile, thus becoming one of the most commonly used intravenous anaesthetics. The high inclination of propofol to gamma-aminobutyric acid receptors is responsible for a considerable pain reduction [24]. Propofol also suppresses sympathetic activity, inhibits the baroreceptor reflex [25] and stimulates nitric oxide production, leading to vasodilation [26].

2.1.1. Pharmacokinetics and Pharmacodynamics

The pharmacokinetic profile of propofol is characterised by a fast distribution from the blood into tissues, a rapid metabolic clearance from the blood and then a slow return of the drug from the peripheral compartment. These processes explain its rapid onset and short duration of action [27].

Intravenous is the only suitable route of administration of propofol: oral bioavailability is, indeed, very low because of a high first-pass effect and high hepatic extraction rate (90%) [28].

After intravenous administration, propofol is bound to the plasma proteins (mostly albumin) and erythrocytes. It is rapidly and extensively distributed to well perfused tissues, including the brain where propofol easily crosses the blood–brain barrier and causes a rapid loss of consciousness [27]. The speed of induction depends on both patient related factors (eg. cardiac output) and speed of infusion. Equilibrium between blood and brain concentrations is reached after 30 minutes and redistribution to lean muscle and fat tissue occurs due to the high lipid solubility of propofol. The context-sensitive decrement time for propofol is generally favourable compared with other hypnotics [29]: in case of a short infusion (3 h), the 80% decrement time is 50 min [30].

The liver is the main site of propofol metabolism, with CYP2B6 and CYP2C9 isoforms being the major catalysts: a maintained hepatic perfusion is, thus, essential to guarantee an efficient metabolism of propofol. Extrahepatic sites of metabolism, predominantly the kidneys and the small intestines, account for 40% of total propofol clearance [31].

88% of propofol is excreted within 5 days in the urine, while a minimal amount through exhalation [30].

Propofol is a sedative hypnotic agent which rapidly and reliably causes loss of consciousness [27].

Propofol's hypnotic effect occurs through potentiation of the effects of the inhibitory neurotransmitter GABA [32]: propofol binds to the b-subunit of the postsynaptic GABA-A receptor, causing inward chloride currents that hyperpolarize the postsynaptic membrane and inhibit neuronal depolarization [30].

Propofol has amnestic properties that mostly affects explicit memory, in a dose-dependent manner, but they are not as marked as those of the benzodiazepines [27,30].

Propofol produces anxiolysis in subhypnotic doses: the mechanism involved is not well defined but seems to be related to inhibition of 5-HT activity in the hippocampus or nitric oxide synthase in the hypothalamus, amygdala and hippocampus [33].

A significant characteristic of propofol is its antiemetic effect, with low incidence and severity of PONV if compared to that associated with other hypnotic drugs. This effect depends on propofol's interaction with dopaminergic (D2) receptors in the chemoreceptor trigger zone, inhibition of the limbic system [34] and the 5-HT3 receptors located in the central nervous system [17].

Since propofol has no analgesic properties, it is often combined with opioids during PSA resulting in a synergistic relationship of sedative and analgesic effects [20].

Propofol decreases cerebral blood flow and metabolic rate and lowers intracranial pressure, while cerebral autoregulation is preserved [27,35].

Propofol shows extensive effects on both cardiovascular and respiratory systems. It causes a reduction of systemic blood pressure and a decrease in cardiac output, effects that appear to be more pronounced in elderly and physiologically compromised patients. The mechanisms responsible for cardiovascular depression are the propofol mediated decrease in sympathetic tone and vascular resistance and the inhibition of the physiological baroreflex responses [36].

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As to the respiratory system, propofol is a potent ventilatory depressant: it reduces the ventilatory responses to hypercapnia and hypoxia, acting at the central chemoreceptor level [37,38]. Propofol also causes upper airway relaxation and suppresses the upper airway reflexes, therefore changing the pattern of breathing [39].

Although the liver and kidneys are highly involved in propofol metabolism and excretion, no functional changes of these organs have been reported [30].

2.1.2. Dosing Regimen

Propofol may be administered as a bolus or an infusion and has a rapid onset of action that is dose-dependent. After a single bolus, the termination of action occurs primarily by redistribution from CNS to peripheral tissues, thanks to the lipophilicity of the drug [40].

For PSA in adults, propofol is administered by slow injection in an initial loading dose of 0.5 to 1 mg/kg IV followed by doses of 0.25 to 0.5 mg/kg IV every one to three minutes until the appropriate level of sedation is achieved [41].

In older adult patients without major comorbidities or hemodynamic instability, propofol, as an ultra-short-acting sedative, is preferred among others to perform PSA. In this type of patients, the dose should be reduced by 20 to 60 percent of a typical healthy young adult dose and administered slower, over three to five minutes, with an initial bolus of no more than 0.5 mg/kg, in order to prevent prolonged sedation and marked cardiorespiratory depression [42].

No dose adjustments are required for propofol in patients with impaired kidney or liver function [43].

Similarly to elderly patients, propofol has a greater volume of distribution also in patients with obesity, therefore in this case the initial dose should be based on the patient's adjusted body weight, followed by additional titrated doses to achieve the desired level of sedation.

Propofol is one of the most widely used medications for paediatric procedural sedation, showing advantages in recovery time compared with other drugs. Evidence suggests propofol has a safety profile similar to alternative sedatives, without excessive concerns for respiratory or cardiovascular adverse events in the paediatric population [44].

2.1.3. Adverse Effects

Owing to propofol's narrow therapeutic index, there is a potentially high risk of adverse events, especially in elderly patients [45].

The best-known side effects include the previously mentioned bradycardia and hypotension, due to myocardial depression, and respiratory depression. These effects generally resolve quickly and uneventfully because of propofol's brief duration of action. However, hypotension can lead to complications in patients with severe medical problems (eg. sepsis, cardiac dysfunction) or hypovolemia [22]. Respiratory depression usually manifests as transient hypoxemia, exacerbated by coadministration of other sedatives or analgesics but is successfully treatable with supplemental oxygen or simple airway maneuvers [46].

Another common but minor adverse effect is pain on propofol injection (POPI), due to irritation of venous adventitia leading to release of mediators such as kininogen from kinin cascade. The use of lidocaine or ketamine, as well as rapid injection of propofol into a large vein, are appropriate precautions to alleviate POPI [47].

Due to propofol's formulation, it should be noticed that hypersensitivity reactions might occur in patients with reported allergies to egg or soy products.

2.2. Ketamine

Ketamine is a dissociative agent, with both analgesic and anesthetic properties, commonly used in emergency medicine for pediatric and adult PSA. It provides sedation, analgesia and amnesia while maintaining upper airway muscle tone, airway protective reflexes, respiratory drive and hemodynamic stability [48].

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Ketamine also provides excellent anesthetic induction and maintenance and can be considered as adjunct/supplement to regional or local anesthesia, thereby enhancing the effectiveness of regional anesthesia.

In combination with propofol, sub-dissociative dosing of ketamine can provide adequate analgesia and possibily fewer complications, if compared with short-acting opioids (eg. fentanyl).

2.2.1. Pharmacokinetics and Pharmacodynamics

Ketamine is an antagonist of N-methyl-D-aspartate (NMDA) receptors and is structurally related to phencycidine.

The drug is highly lipid soluble: this characteristic results in extensive distribution to peripheral sites (including the CNS) as evidenced by its relatively large Vd [17].

Ketamine shows a chiral structure consisting of two optical isomers. The use of S-ketamine is increasing worldwide, since the S(+)-enantiomer has been postulated to be a four times more potent anesthetic and analgesic than the R(-)-enantiomer and approximately two times more effective than the racemic mixture of ketamine [49].

Absorption of ketamine is rapid though the rate of uptake and bioavailability is determined by the route of exposure [48].

Intravenous ketamine has low oral bioavailability, due to its extensive first-pass metabolism with conversion to the active metabolite norketamine [17] by cytochrome P450. Ketamine is metabolized via the hepatic system, with a half-life of approximately 45 minutes [50], and it is primarily eliminated by the kidneys, though unchanged ketamine accounts for only a small percentage in the urine [48].

Similar to propofol, ketamine is used as a sedative drug for short painful procedures such as fracture reduction or laceration repair in the ED, due to its rapid onset, relatively short duration of effect (10-20 minutes) and excellent sedative and analgesic properties [23,51].

The underlying pharmacology of ketamine is different from that of other procedural sedation and analgesia agents. Ketamine causes dissociation between the thalamocortical and limbic systems and thus prevents patients from perceiving sensory stimuli (eg. pain, sight, sound) [23]. This results in a trancelike cataleptic state of sensory isolation, characterized by potent analgesia, sedation and amnesia while preserving cardiovascular stability and spontaneous respiration and protective airway reflexes. This unique dissociative action and the partial agonism on opiate mu-receptors permit the performance of painful procedures in a consistent state of sedation and patient comfort [52,53].

Ketamine may also interact with sigma receptors and decreases central sensitization, wind-up phenomenon (development of ongoing, worsening or chronic pain) and pain memory [50].

Ketamine might be used at low dose to potentiate opioid-induced analgesia and prevent opioid-induced acute hyperalgesia and tolerance [54].

2.2.2. Administration

Ketamine can be administered either IV or IM. In the first case, the onset of action is within 30-60 seconds while it takes approximately 4 minutes when administered IM, with a duration of action from 15 to 30 minutes [50]. The IV route is preferable, especially for adults, because recovery is faster and the emetic effect is lower. The IM route is useful in case of difficulty obtaining an IV access and for patients who are uncooperative or combative (eg. mentally disabled patients) [55].

The dosing regimen varies according to the desired effect, the patient's age and underlying conditions. Children metabolize the drug more rapidly than adults and require higher or additional dosing; elderly patients appear to have a lower clearance and prolonged duration of action, therefore they need lower dosing [17].

Instead of a dose-response continuum observed with all other PSA agents, ketamine dissociation appears at a dosing threshold of approximately 1 to 1.5 mg/kg intravenously or 3 to 4 mg/kg intramuscularly. When given in smaller doses, ketamine exhibits analgesia and disorientation. Once the dissociative threshold is reached, additional ketamine does not influence the level of sedation, as would be the case with opioids, sedative-hypnotics or inhalational agents [55].

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The initial IV dose of ketamine for procedural sedation ranges from 0.5 to 2 mg/kg, administered over 30-60 seconds, for adults. Subsequent doses of 0.25 to 1 mg/kg may be repeated every 5 to 10 minutes afterwards, depending on if other anesthetic and/or analgesic medications are concomitantly administered [56].

For children, the guidelines recommend administering 4 to 5 mg/kg IM with repeated full or half doses after 5 to 10 minutes if necessary [55].

Like propofol, no dose adjustments are required for ketamine in patients with impaired kidney or liver function. For obese patients, it is recommended to use AdjBW to determine the initial dosing of ketamine and additional titrated doses as needed, to prevent side effects and oversedation [57].

Tonic-clonic movements may present during the administration of ketamine; nonetheless, they do not mean that additional doses of the anesthetic are required [50].

2.2.3. Ketofol

In the context of PSA, a recently emerging strategy is to combine ketamine and propofol, obtaining the so called "ketofol", to create a synergistic sedation state.

Several small prospective trials have studied this combination, suggesting that it may lead to a more stable procedural sedation state and be well tolerated [58]. In addition to that, the intravenous combination tipically allows lower drug dosing compared to that necessary with either propofol or ketamine used as a sole agent, thus reducing the potentially associated adverse risks [15].

Ketofol showed less respiratory adverse effects than propofol alone in emergency department PSA [23]. Similarly, the risk for ketamine-associated nausea and vomiting and emergence reactions are purportedly reduced by the antiemetic and axiolytic properties of propofol [15].

There is no standard for mixing or dose regimen; a common approach is to mix 10 mg/mL ketamine and 10 mg/mL propofol into a 20-mL syringe. The initial dose is 0.375 to 0.5 mg/kg (0.0375 to 0.05 mL/kg of this mixture), and half of this dose can be repeated as needed.

Ketamine is preferable to propofol when hypotension is of particular concern. It should also be chosen in patients with a significant tolerance to GABAergic agents, for procedures longer than 5-10 minutes and when the maintenance of airway protective reflexes is critical.

2.2.4. Adverse Effects

Ketamine is a useful medication in procedural sedation; however, careful attention should be made in patient selection [56].

The most common side effects associated with ketamine include emesis, tachycardia and hypertension, emergence reactions, hypersalivation, transient laryngospasm, increased intracranial and intraocular pressure, muscular hypertonicity and random, purposeless movements (especially in children) [55,59].

Emergence reactions are among the most reported side effects of ketamine, occurring in up to 20% of adults [59]. They have been described as disorientation, vivid dreams and hallucinations, which are often benign and self-limited. Emergence reactions can be promptly and effectively treated with small doses of benzodiazepines such as midazolam or even prevented with midazolam or haloperidol pretreatment [60].

Mild to moderate transient increases in blood pressure, heart rate and cardiac output are common effects due to ketamine's increase in sympathetic activity [56]. On one hand, this anti-shock effect might be helpful to avoid peri-procedural hypotension; on the other, these cardiovascular changes rise concern of an elevated mycardial oxygen demand that could potentially exacerbate underlying cardiac disease. Ketamine is included in the American Heart Association (AHA) list of medications that may cause or exacerbate heart failure and has been reported to precipitate myocardial ischemia in the elderly [61,62]. The real incidence of myocardial ischemia after ketamine administration is unknown; however, ketamine avoidance is recommended for patients with known coronary artery disease, older adults with CAD risk factors or those who are already hypertensive or tachycardic [55].

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Laryngospasm is a rare complication, occurring more frequently in children than adults, and is typically either transient or improves with bag-mask ventilation. The risk is greater in patients with anatomic abnormalities of the upper airway (eg. tracheal stenosis, tracheomalacia).

As to the emetic effect, pretreatment with ondansetron or comparable agents may be helpful to prevent nausea and vomiting associated with ketamine use.

Absolute contraindications for ketamine administration are an age younger than 12 months - for the higher risk of airway complications - and known or suspected schizophrenia - due to the risk of exacerbation of this condition -.

Relative contraindications include: major procedures stimulating the posterior pharynx (eg. endoscopy); history of airway instabiity, tracheal surgery or tracheal stenosis (possibile higher risk of airway complications); active pulmonary infections or disease, included asthma; known or suspected cardiovascular disease (exacerbation caused by sympathomimetic properties of ketamine); CNS masses, abnormalities or hydrocephalus (increased intracranial pressure with ketamine); glaucoma or acute globe injury (increased intraocular pressure with ketamine); porphyria, thyroid disorder or medication (enhanced sympathomimetic effect) [55].

Overall, ketamine remains a safe medication option in adults undergoing procedural sedation [56].

2.3. Dexmedetomidine

Dexmedetomidine is a commonly used alternative to propofol for PSA in adults and has demonstrated to be an efficacious and safe adjuvant to other sedative and anesthetic medications during surgical procedures and in intensive care unit. In this context, dexmedetomidine has shown to consistently reduce opioids, propofol and benzodiazepines requirements [63].

2.3.1. Mechanism of Action

Dexmedetomidine is a highly selective and potent alpha-2 adrenergic agonist with a dose-dependent effect that ranges from minimal to deep sedation [64]. It acts on presynaptic alpha-2 receptors at the locus coeruleus in the pons to reduce release of norepinephrine, therefore the activity of the sympathetic nervous system [65]. It also appears to reduce pain through modulation of alpha receptors in the spinal cord [63].

Dexmedetomidine has remarkable pharmacological properties including sedation, anxiolysis and analgesia [63].

It induces a unique sedative response, similar to natural sleep and known as “arousable sedation” or “cooperative sedation”, which shows an easy transition from sleep to wakefulness, thus allowing the patient to be cooperative and communicative when stimulated [66].

The analgesic effect is mediated by several mechanisms, including alpha2-receptor binding in central and spinal cord. Pain transmission is suppressed by hyperpolarization of interneurons and reduction of the release of pronociceptive transmitters such as substance P and glutamate [67].

Despite dose-related sedation, memory and cognitive functions are not severely impaired with dexmedetomidine administration [68].

Dexmedetomidine has cardiovascular effects, producing a typical biphasic response with hypotension at low plasma concentrations and hypertension at higher plasma concentrations [69]. The IV loading dose, which corresponds to the peak plasma concentration, leads to a transient increase in blood pressure, most likely due to vasoconstriction induced by the stimulation of peripheral α-2B receptors in vascular smooth muscle, and reflex bradycardia, mediated by a reduction in norepinephrine level and caused by the baroreceptor reflex [70]. After a few minutes, when dexmedetomidine plasma concentrations decrease, hypotension occurs as the vasodilatory effects of the central α-2A receptors and the enhanced vagal activity predominate [71]. Bradycardia and hypotension can be easily managed with atropine and vasoactive agents or prevented by decreasing loading dose sizes or administration time interval [69].

Several small trials revealed that the combination of dexmedetomidine with ketamine (1 to 2 mg/kg) can provided effective procedural sedation while minimizing cardiovascular depression [72].

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Unlike other sedatives or anesthetics, dexmedetomidine is responsible for minimal respiratory depression, even at higher doses [68]. However, it has been shown to rarely cause apnea and to impair the respiratory responses to hypoxia and hypercapnia [73].

Dexmedetomidine has minimal effect on cerebral hemodynamics, including cerebral blood flow and brain tissue perfusion; however, it may modestly reduce ICP, due to its mild cerebral vasoconstriction effects, reduction in cerebral blood volume and in cerebral metabolic rate [74].

Dry mouth is a reported side effects of dexmedetomidine [70].

2.3.2. Pharmacokinetics

A high inter-individual variability in dexmedetomidine pharmacokinetics has been described, with several factors, such as body size, hepatic impairment, plasma albumin and cardiac output, having a significant impact on it [69].

Multiple routes of administration have been investigated, although the only dexmedetomidine registered use is intravenously. The extravascular administration (oral or intranasal) might be useful for uncooperative children or geriatric patients and to avoid the high peak plasma levels normally seen after IV administration.

Dexmedetomidine presents an extensive first-pass effect, with a bioavailability of 16%, when absorbed through the buccal mucosae [75]. The drug is rapidly distributed throughout the body, readily crossing the blood-brain barrier and also placenta barriers. Dexmedetomidine is mainly hepatically metabolized into inactive metabolites by glucuronidation and hydroxylation: elimination occurs through the kidneys (95%) and feces (4%). Less than 1% of dexmedetomidine is excreted unchanged [69].

2.3.3. Administration

When used as a sedative agent, dexmedetomidine is given as an infusion at the rate of 0.2- 1 mcg/kg/hour, for both adults and children. A bolus of 0.5 to 1 mcg/kg can be given over 10 minutes prior to starting infusion. Patients with liver disease, as well as obese patients, require lower starting doses [76]. The onset time of IV dexmedetomidine is in 3 to 5 minutes while the effects last 15 minutes [77]. Dexmedetomidine can also be given intranasally in doses of 2 to 3 mcg/kg for anxiolysis and sedation when other routes of administration are not regarded as optimal choices.

2.3.4. Contraindications and Monitoring

There are no absolute contraindications to the use of dexmedetomidine. It should be used cautiously in patients with bradycardia and hypotension and with known heart failure as there is level B evidence showing dexmedetomidine might exacerbate myocardial dysfunction [78].

As with other sedative agents, heart rate and rhythm, blood pressure, pulse oximetry and the level of sedation require close monitoring [78].

In conclusion, thanks to its short half-life and low respiratory effects, dexmedetomidine can be considered as a reasonable choice for PS in the ED [65].

2.4. Fentanyl

Short-acting opioids, such as fentanyl, alfentanil and remifentanil, are often given alone or in combination with sedatives to carry out PSA.

After being synthesized more than 60 years ago, fentanyl has become the opioid most commonly used intravenously for intraoperative analgesia [79]. This fact has occurred due to its minimal cardiovascular effects, absence of histamine release, relatively short action and for being easily and inexpensively prepared for the marketplace [80].

Fentanyl was frequently coadministered with midazolam to provide analgesia during PSA before propofol and etomidate became widely available [79]. However, this combination is still used in settings where ultra-short-scting agents are unavailable or a longer duration of PSA is required (eg. gastrointestinal endoscopy) [15].

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2.4.1. Pharmacology and Pharmacokinetics

Fentanyl is a synthetic potent lipid soluble opioid. It is a mu-selective opioid agonist that produces analgesia and also has the capability to activate other opioid system receptors like the delta receptors and potentially the kappa-receptors [80].

Fentanyl has 75 to 125 times the potency of morphine, a rapid onset of action (1 to 3 minutes) and a short duration of effect (30 to 60 minutes) but has no amnestic properties [80].

Many reports have shown important pharmacokinetic differences between alfentanil, fentanyl and sufentanil, the first one having the most rapid analgesic onset and time to peak effect as well as the shortest distribution and elimination half-lives. The pharmacokinetic properties of opioid analgesics can be influenced by factors like patient age, plasma protein content, acid-base status, changes in hepatic blood flow and administration of competitive drugs but not by renal insufficiency [81].

Fentanyl is highly lipophilic and strongly binds to plasma proteins. It has a large volume of distribution (3,5-8 L/kg) and a high clearance (30-72 L/h) [82].

When given as an intravenous bolus, fentanyl is rapidly distributed from plasma into highly vascularized compartments and presents a rapid redistribution from the central nervous system to muscle and fat tissue [80].

Fentanyl is hepatically metabolized via the CYP450 enzyme system, specifically CYP3A4, through an N-dealkylation that results in the inactive metabolite norfentanyl. Less than 1% is metabolized by alkyl hydroxylation, N-dealkylation or amide hydrolysis to the inactive compounds hydroxyfentanyl, hydroxynorfentanyl and despropionylfentanyl.

Fentanyl has a half-life of 3 to 7 hours. Excretion occurs for 75% in the urine and 9% in feces [81].

2.4.2. Dosing Regimen

Opioid analgesics are mainly administered using the intravenous route. Still, other techniques of administration, including epidural, intrathecal, transdermal and intranasal applications, have been demonstrated [80]. Fentanyl is a rapid-acting drug when given via transmucosal or intravenous routes while the transdermal administration shows a slower onset and a longer duration of effect [83].

When used in combination with a sedative for PSA, fentanyl is given intravenously at 1 to 1.5 mcg/kg initial dose and then titrated 0.5-1 mcg/kg every 3 minutes until the appropriate level of sedation and analgesia is achieved [83]. The maximum total dose is generally 5 mcg/kg or approximately 250 mcg, but higher doses may be needed in some instances. AdjBW, instead of ABW, is recommended to be used to determine the initial dose and subsequent titration for obese patients, in order to lower the magnitude of potential side effects [57].

The frequently used combination of midazolam and fentanyl is associated with a significant risk of hypoxia and apnea, which may require airway intervention and medication reversal [84]. To minimize the risk of respiratory depression, a reasonable approach to dosing suggests administering midazolam first (0.02 mg/kg), followed by fentanyl (0.5 mcg/kg), with careful titration. The patient response should be monitored before each administration. Smaller doses and longer intervals between doses are required for older patients and in case of hepatic or renal dysfunction.

2.4.3. Contraindications and Adverse Effects

The use of fentanyl is contraindicated in the following situations: patients with respiratory depression or obstructive airway diseases, liver failure, known intolerance or hypersensitivity to fentanyl or other morphine-like drugs or any components present in the formulation, MAO use in the previous 14 days [82].

Fentanyl should not be taken concomitant with CYP3A4 inhibitors, such as macrolide antibiotics or azole-antifungal agents, because of potential drug interactions. Protease inhibitors and the cessation of a CYP3A4 inducer medication (eg. carbamazepine, phenytoin) should also be avoided

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since they might increase fentanyl plasma concentrations, thus facilitating opioid-related adverse effects and cause potentially fatal respiratory depression [81,82].

The primary side effect of opioids is respiratory depression that appears to be potentiated by the coadministration of sedatives.

Like morphine, meperidine and others, fentanyl produces the typical mu opioid central nervous system actions such as fatigue, sedation, nausea and vomiting, dizziness, bradycardia (due to a central vagal stimulating action). Fentanyl has less hemodynamic effects, therefore is indicated in case of hypotension, and the incidence of constipation and pruritus is lower than that caused by morphine and most of non-fentanyl mu receptor-stimulating opioids [80].

The elderly and patients with renal or hepatic dysfunction can experience more prolonged or profoud adverse effects.

A reversal drug, Naloxone, is available to effectively terminate fentanyl effects when necessary [80].

2.5. Midazolam

Midazolam is the most frequently used benzodiazepine for procedural sedation. It is reported to be 2 to 6 times as potent as diazepam [84].

Midazolam might be used alone for anxiolysis; however, as it has no analgesic properties, it is typically combined with short-acting opioids (eg. fentanyl) for deeper levels of sedation and analgesia [20].

2.5.1. Pharmacology

The actions of benzodiazepines such as midazolam are mediated through the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). These drugs bind to the benzodiazepine site on GABA-A receptors, which potentiates the effects of GABA by increasing the frequency of chloride channel opening, and thereby producing a sedating effect, muscle relaxation, anxiolysis, anterograde amnesia and also an anticonvulsant action.

Midazolam has a rapid onset time of 2 to 3 minutes but the effect site concentration peaks only after approximately 13 minutes [64]. The duration of action is longer than propofol (20 to 80 min) and with a prolonged half-life: for this reason, midazolam is used mainly for shorter procedures but with caution in elderly patients or patients with comorbidities [20].

Midazolam has both hydrophilic and lipophilic properties, depending upon the pH [85] and can easily and quickly penetrate the blood-brain barrier.

2.5.2. Pharmacokinetics

The pharmacokinetic parameters of midazolam are variable and depend on factors such as age, bodyweight, hepatic and renal function. In the elderly, obese patients and those with hepatic impairment, midazolam has a reduced clearance and prolonged half-life. Since midazolam is highly protein bound, hypoalbuminaemia leads to a higher free fraction of midazolam and increased distribution of the drug in the CNS, resulting in a greater sedation effect [17].

Midazolam has poor oral absorption and both in adults and pediatric patients the drug is approximately 97% bound to plasma protein, principally albumin.

Midazolam metabolism occurs via hepatic CYP450 enzymes and glucuronide conjugation. The 1-hydroxy-midazolam metabolite comprises 60-70% of the biotransformation products of midazolam and it is as potent as the parent compound, contributing for 10% to the net pharmacologic activity of midazolam.

The amount of midazolam excreted unchanged in the urine when given intravenously is less than 0.5%, with an elimination half-life of 1.5 to 2.5 hours. 45% to 57% of the dose is excreted in the urine as 1-hydroxymethyl midazolam conjugate.

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2.5.3. Administration and Dosage

Midazolam administration can be through oral, intranasal, buccal, intravenous and intramuscular routes. For PSA, midazolam is usually administered IV over 1 to 2 minutes in doses of 0.02 to 0.03 mg/kg. The total dose required for adequate sedation varies based upon many factors, including patient weight and age, medication tolerance, comorbidities and the duration of the procedure. Often in adults, midazolam is given in individual doses of 0.5 or 1 mg and titrated to effect. No single dose should exceed 2.5 mg and repeat doses may be given every 2 to 5 minutes as necessary. In most cases, PSA can be performed using no more than 5 mg of midazolam. Sedation in adult and pediatric patients is achieved within 3 to 5 minutes after IV injection.

For children 1 to 5 months old, the intranasal route is recommended at the dose of 0.2mg/kg. For children 6 months and older, the necessary dose is about 0.2 to 0.3 mg/kg intranasally [85].

Patients over 65 years of age and those with hepatic or renal dysfunction have a decreased clearance of midazolam, therefore they should receive reduced doses (approximately half the dose used in younger patients), longer dosing intervals and should be monitored for excessive sedation [17].

Patients with cardiovascular diseases should undergo a systematic and careful evaluation of their physical status and cardiac reserve, before performing PSA. However, in emergency procedures (eg. gastroscopy for bleeding) this evaluation might have to be limited. Current practice suggests providing PSA with benzodiazepine (mainly midazolam) and/or propofol, and low-dose opioid, especially for minor or major cardiac procedures such as left heart catheterisation or coronary stenting, electrical cardioversion and implantation of internal defibrillators, pacemakers or trans-femoral aortic valves [20].

The half-life and volume of distribution of benzodiazepines increases with body weight, therefore the medication and metabolites have the potential to accumulate with additional doses and cause adverse effects, mainly oversedation and respiratory depression, in case of obesity. Recommendations are to determine the initial dose according to the AdjBW of the patient, and to administer smaller supplemental doses as needed until the desired effect is achieved [57].

2.5.4. Adverse Effects and Monitoring

The primary drawback of midazolam is the potential for accumulation of the drug, mostly in adipose tissue, with repeated doses, which can significantly prolong sedation [17].

While midazolam is thought to cause minimal hemodynamic effects, it has the potential to induce loss of airway reflexes, respiratory depression, and even apnea. Respiratory depression can happen with a dose of 0.15 mg/kg and the risk is increased when midazolam is given concomitantly with other sedatives or opioids, such as fentanyl [64].

Several studies suggest that the incidence of bradycardia, hypotension and hypoxia is higher with the use of midazolam/opiate, if compared to other sedatives or analgesics for PSA, and can occur primarily in case of rapid IV administration [16].

Other common adverse effects associated with midazolam include hiccoughs, cough, nausea and vomiting, thrombophlebitis or pain on injection.

As previously stated, in elderly patients it is necessary to pay attention to the triggering of benzodiazepine-induced neurocognitive alterations, with an increased risk for drowsiness, ataxia, falls and confusion.

Monitoring is essential for elderly individuals and patients with liver and kidney disease and is also necessary for drug interactions with erythromycin, clarithromycin, diltiazem, sertraline, protease inhibitors, rifampin, phenytoin, phenobarbital, carbamazepine, opioids, antipsychotics and alcohol [85].

When necessary, flumazenil is a reversal agent available to terminate the effects of midazolam or other benzodiazepines.

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2.6. Etomidate

Etomidate is an ultra-short-acting, non-barbiturate hypnotic intravenous anesthetic agent [86]. It has been approved for induction of general anesthesia, rapid sequence intubation and short operative procedures such as reduction of dislocated joints, tracheal intubation, cardioversion, dilation, curettage or cervical conization [87,88].

Several randomized trials and prospective observational studies have found that etomidate is an effective sedation agent for PSA and it is not associated with major complications [89].

2.6.1. Pharmacology and Pharmacokinetics

Etomidate is an imidazole derivative, structurally unrelated to other anesthetic agents. It produces its effect by acting as a positive allosteric modulator on GABA-A receptors by binding directly to specific sites and increasing the affinity of the inhibitory neurotransmitter GABA (positive modulation of GABA-mediated activity) [88].

Its action at the level of the reticular-activating system produces anesthesia. Etomidate seems to have disinhibitory effects on the parts of the nervous system that control extrapyramidal motor activity: these effects might explain the incidence of myoclonus during induction with this drug [86].

Etomidate is registered for intravenous use only, although other routes of administration have been investigated for sedative or anxiolytic purposes.

Like most intravenous anesthetics, etomidate is highly protein-bound (77%). As a consequence, in low albumin states (eg. hepatic or renal insufficiency) more free-drug is available and reaches higher concentrations in the brain.

The volumes of distribution are relatively large, likely owing to etomidate high solubility in fat, and seem to be related to body weight [90].

Etomidate induces unconsciousness within one circulation time; recovery is rapid as a result of extensive redistribution and rapid metabolism.

Metabolism is primarily hepatic by ester hydrolysis to inactive metabolites. These metabolites are excreted in urine and for a small part in bile; less than 2% of etomidate is excreted unchanged [90].

2.6.2. Administration and Dosage Regimen

Etomidate is an intravenous agent that offers several advantages: simple dose regimen, fast onset of action, short duration of effect, rapid metabolism, low risk of histamine release, hemodynamic stability on bolus injection [88].

It has a favorable hemodynamic profile on induction, with minimal blood pressure depression, therefore being ideal for shock trauma, hypovolemic patients or patients with significant cardiovascular disease [91].

For PSA in adults, etomidate is administered IV over 30 to 60 seconds in doses of 0.1 to 0.15 mg/kg (lower than the rapid sequence intubation dose). It can be redosed at 0.05 mg/kg approximately every 3 to 5 minutes as needed [51,92]. The onset of action of etomidate is almost immediate and its duration of effect seems to be directly correlated to the dose (with each 0.1 mg/kg providing about 100 seconds of unconsciousness), so approximately 5 to 15 minutes at the usual dosage for adults [86].

Since etomidate is primarily excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with renal dysfunction. Because elderly patients are more likely to have decreased renal function, doses in the lower dosing range should be used in this group and clinicians should monitor kidney function [86]. No dosage adjustments are required in case of hepatic impairment.

Etomidate has pharmacokinetic and pharmacodynamic properties similar to propofol; hence, obesity requires dosing to be based on AdjBW of the patient with additional titrated doses given as needed [57].

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2.6.3. Medication Choice

With propofol, etomidate is one of the preferred medications for PSA in healthy and hemodynamically stable patients. Both drugs are safe and effective and have similar times to onset and recovery. Propofol may cause hypotension or decreased cardiac function, therefore etomidate is preferable for patients in whom hypotension is a particular concern, since it provides greater hemodynamic stability. Nevertheless, etomidate might be responsible for myoclonus (which appears to reduce the rate of procedural success) and dose-dependent adrenal suppression (which may be harmful in patients with critical illness) [92]. Evidence also suggests that etomidate might be more likely associated with post-procedural nausea and vomiting [93].

Etomidate has no analgesic properties and often requires the coadministration of a short-acting opioid (eg. fentanyl), which increases the risk of respiratory depression [51]. In this setting, recommendation is not to exceed 0.5 mcg/kg of fentanyl in any single dose when given with etomidate and to keep the total amount of fentanyl to a minimum.

2.6.4. Adverse Effects

Potential side effects of etomidate include myoclonus, adrenal suppression, nausea and vomiting.

One of the most common adverse reaction associated with etomidate is transient intravenous pain on injection, especially into peripheral and small vessels. Strategies similar to those used for propofol can be used to reduce such pain, as for example prior IV injection of lidocaine [86].

Myoclonus is thought to be related to subcortical disinhibition and might be observed in up to 80% of the patients receiving PSA. The degree of myoclonus may be dose dependent and ranges from mild and transient to severe enough to prevent completion of the procedure; however, severe forms rarely occur during PSA. If necessary, midazolam 1 to 2 mg IV approximately every 60 seconds is the recommended treatment until myoclonus abates. According to several studies, pretreatment with midazolam, dexmedetomidine, fentanyl, propofol or ketamine reduces myoclonus incidence and severity after a bolus dose of etomidate [86,94].

Etomidate causes adrenal insufficiency when given by continuous infusion; nonetheless, reductions in plasma cortisol concentrations have also been reported in patients receiving a single induction dose of etomidate [95]. The clinical significance of these transient reductions in cortisol in patients undergoing PSA with etomidate remains unclear and complications related to adrenal suppression have not been reported.

The incidence of PONV is higher when etomidate is used for both induction and maintenance of anesthesia in short procedures [86].

The brief duration of action of etomidate is associated with a reduced risk for adverse respiratory events. No serious complications have been reported with the use of etomidate; nevertheless, clinicians must be prepared to support the patient's airway and breathing in the event of respiratory compromise.

2.7. Nitrous Oxide

Nitrous oxide (N_2O) is an analgesic and anxiolytic gas causing CNS depression and euphoria with little effect on the respiratory function. It is an ultra-short-acting agent with an immediate onset of action and a fast recovery (due to its low blood solubility), and it provides analgesia, anxiolysis and sedation. It leads to a state of euphoria, explaining its nickname “laughing gas” [96].

Nitrous oxide can be used for general anesthesia, procedural sedation, dental anesthesia (especially in the pediatric setting) and to treat severe pain. Its potent analgesic properties are useful in providing analgesia in settings such as the obstetrical ward or emergency department [96].

Studies in children have generally found N_2O to be safe, but it may not provide adequate analgesia for more painful procedures such as fracture reduction.

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2.7.1. Pharmacology and Pharmacokinetics

Nitrous oxide is an odorless, colorless, non-flammable gas. It is the least potent inhalational anesthetic: it requires a concentration of 104% to reach one minimum alveolar concentration (MAC), thus is often administered in combination with a more potent and volatile anesthetic.

Nitrous oxide has multiple supraspinal and spinal targets. The anesthetic effect is mediated by its non-competitive NMDA inhibition in the central nervous system. The analgesic effects, comparable to morphine, occur by releasing endogenous opioids that act on opioid receptors. GABA-A receptors activation produces N_2O's anxiolytic effects. Nitrous oxide has a central sympathetic stimulating activity that supports blood pressure, systemic vascular resistance and cardiac output. It also stimulates cerebral blood flow and increases intracranial pressure [97].

Compared to other anesthetic agents, nitrous oxide has minimal effects on the respiratory and cardiovascular systems. It leads to decreased tidal volume and increased respiratory rate but minimizes overall minute ventilation. N_2O leads to direct myocardial depression but the sympathetic stimulation reduces this effect, thus the net effect is minimal. Unlike other volatile anesthetics, nitrous oxide has no muscle relaxation properties [98].

As to the pharmacokinetic properties, inhaled N_2O is rapidly absorbed through alveoli, with an onset of action within 2 to 5 minutes [99]. Because of its rapid diffusion across alveolar basement membranes, compared to other gases, N_2O may produce the second gas effect. Its rapid exit from the alveoli results in remaining alveolar gases being concentrated, thus accelerating N_2O uptake into the blood and speeding the onset of anesthesia.

Nitrous oxide is metabolized through reduction by anaerobic bacteria in the gut and it is primarily eliminated via the lungs [96].

2.7.2. Administration

Nitrous oxide administration occurs via inhalation using a simple face mask, laryngeal mask airway or an endotracheal tube.

For surgical PSA and dental procedures, N_2O is combined with oxygen: usually, the patient receives 100% oxygen at the beginning of the procedure, then oxygen is slowed and N_2O incrementally increased. No standard therapeutic levels exist but the concentration of nitrous oxide should not routinely exceed 50% [100]. A flow rate of 5 to 6 L/min is generally acceptable to most patients. This approach is contraindicated in COPD, severe emotional disturbances or drug-related dependencies, during the first trimester of pregnancy, treatment with bleomycin sulfate, recent tympanic membrane graft and MTHFR deficiency [96].

No specific information about dose adjustment for patients with renal or hepatic impairment are available.

2.7.3. Adverse Effects

Adverse effects of nitrous oxide include:

- Diffusion hypoxia: after discontinuation of nitrous oxide, the concentration gradient between the gases in the lung and alveolar circulation rapidly reverses, leading to rapid oxygen dilution in the alveoli and subsequent hypoxia. 100% oxygen administration should follow nitrous oxide cessation [96].
- Respiratory Depression: N_2O has limited respiratory effects but it can potentiate the respiratory depressant effects of other sedatives, hypnotics or opioids when coadministered [96].
- Subacute myeloneuropathy: nitrous oxide use disorder can cause a severe but potentially reversible myeloneuropathy characterized by axonal sensorimotor neuropathy [101].
- Nausea and vomiting: nitrous oxide seems to have a higher risk of PONV compared to other agents, but it can be controlled with prophylactic anti-emetics [102].
- Hyperhomocysteinemia: N_2O irreversibly oxidizes the cobalt atom of vitamin B12 and reduces the activity of vitamin B12-dependent enzymes (eg. methionine synthetases) which can also lead to megaloblastic anemia [96].

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2.8. Remimazolam

Remimazolam is a novel short-acting benzodiazepine approved for intravenous procedural sedation and general anesthesia [103]. In particular, remimazolam is indicated for the induction and maintenance of PS in adults undergoing procedures lasting 30 minutes or less.

Due to its fast onset, short and predictable duration of sedative action, short recovery time, rare accumulation after long-term infusion and less serious side effects, compared with other benzodiazepines, remimazolam is a promising sedative for use among a wide range of patients, critically ill ones included [103].

2.8.1. Chemical Structure

Remimazolam is a member of the benzodiazepine class of drugs, whose properties are a combination of two existing drugs used in anesthesia: midazolam and remifentanil.

Its structure is similar to midazolam and was modified to produce an agent with an organ-independent metabolism.

It is an ultra-short-acting drug, with a faster recovery if compared to midazolam [104], that achieves peak sedation within 3 to 3.5 minutes after IV administration: this characteristic makes remimazolam desirable for use during short procedures.

Like other benzodiazepines, remimazolam exerts its therapeutic action by potentiating the effect of gamma-aminobutyric acid on GABA-A receptors, the main inhibitory neurotransmitter receptors in the mammalian brain, as a positive allosteric modulator.

2.8.2. Pharmacokinetics and Pharmacodynamics

Remimazolam is rapidly distributed upon intravenous administration and it is >91% protein-bound in plasma, primarily to serum albumin. Following intravenous administration, its distribution half-life is 0.5 - 2 minutes and the terminal elimination half-life is 37 - 53 minutes.

Remimazolam does not appear to undergo biotransformation via hepatic cytochrome P450 enzymes, nor does it induce or inhibit these enzymes, thus clinically significant metabolic drug interactions are unlikely [103].

Remimazolam is susceptible to non-specific tissue esterases and it is rapidly metabolized into its pharmacologically inactive metabolite CNS-7054 [104], which has 300-fold lesser affinity for GABA-A receptors as compared to the parent drug. This mechanism is responsible for the ultra-short-action of the drug.

In healthy subjects, about 80% of the administered dose is excreted in the urine as CNS-7054.

Remimazolam showed no significant effects on the PR interval and QRS duration, nor on cardiac repolarization during PSA and anesthesia [105]. Moreover, remimazolam has no clinical effects on heart rate, blood pressure and respiratory rate [103].

2.8.3. Administration

For procedural sedation in adults, remimazolam is administered IV at the dose of 5 mg over 1 minute; for maintenance, supplemental doses of 2.5 mg should be administered over a 15 second time period, after at least two minutes.

For induction, in ASA (American Society of Anesthesiologists) class III and IV patients, recommendation is to use 2.5 mg to 5 mg IV over 1 minute based on the clinical condition, followed by 1.25 mg to 2.5 mg intravenously as needed over 15 seconds, to maintain PSA [106].

Liver dysfunction can result in elevated serum levels of remimazolam, therefore patients with severe hepatic impairment should be carefully titrated to effect.

No significant differences were observed in the pharmacokinetics of remimazolam between healthy individuals and patients with end-stage renal disease. Remimazolam can be safely used in patients with varying degrees of renal impairment without any requirement for dose adjustment [103].

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Lower doses of infusion should be considered for the fragile elderly or ASA class 3+ patients, although the pharmacokinetic of remimazolam is unaffected by age, ASA class, sex, and race [103].

2.8.4. Adverse Effects

Remimazolam exerts little influence on the cardiovascular and respiratory systems. It is associated with a low risk of hypotension and respiratory depression, with a small fluctuation range of blood pressure and heart rate. It does not cause severe injection site pain; on the contrary, pre-treatment with remimazolam is known to reduce the incidence and intensity of propofol-induced injection pain.

Owing to its organ-independent metabolism and its first-order pharmacokinetics, the degree and duration of remimazolam sedation are dose-dependent, thus long-term infusions or higher doses will not result in cumulative and extended sedative effects [107].

Remimazolam is not cause of fatal or severe adverse effects during the infusion phase and, if needed, its effects can be reversed by flumazenil.

3. Techniques and Monitoring in Procedural Sedation and Analgesia

Sedation and analgesia comprise a continuum of states ranging from minimal sedation (anxiolysis) through general anesthesia, however it is not always possible to maintain patients at a pre-determined sedation depth.

Sedation levels [1,2,5] can be divided into (Table 1):

- Minimal: a drug induced state of diminished anxiety, during which patients are conscious and respond purposefully to verbal commands or light tactile stimulation. Cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are unaffected. In the Emergency Department this level is most often achieved through inhaled mixtures of nitrous oxide and oxygen;
- Moderate: a drug induced state of depressed consciousness, during which patients retain the ability to respond purposefully to verbal commands or light tactile stimulation. During moderate sedation, no interventions are normally required to maintain a patent airway and spontaneous ventilation is adequate. Cardiovascular function is usually maintained. Event amnesia will frequently occur under moderate sedation levels. In the Emergency Department this level is most often achieved using a combination of opioids and benzodiazepines;
- Deep: a drug induced state of depressed consciousness during which patients are not easily aroused and may respond only to noxious stimuli. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained. Nonetheless, deep sedation carries the risk for loss of airway patency, depression of protective airway reflexes and of the respiratory centers, and depression of the cardiovascular system.

Table 1. Levels of Sedation.

Level of sedation	Consciousness and responsiveness	Airways and ventilation	Cardiovascular system
Minimal	Patient is conscious Response to verbal stimuli	Preserved	Unaffected
Moderate	Depressed + Response to verbal or tactile stimuli	Preserved	Usually unaffected
Deep	Depressed ++ Response to repeated or painful stimuli	May require assistance	Affected

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A further separate sedation category is defined by dissociative sedation, a trancelike cataleptic state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respiration, and cardiovascular system stability. In the Emergency Department this level is most often achieved through the use of ketamine [2–4].

The initial drug dose should be determined after having performed a careful pre-sedation assessment of the patient's status. Further titration of the selected drug(s) to optimal effect is critical to safely achieving the established sedation endpoint, thereby minimizing the risk of inadvertent over-sedation.

Whenever feasible, a pre-sedation assessment should be conducted, and it should comprise a focused medical history, physical examination with airway evaluation to rapidly identify a potentially difficult airway, a review of comorbidities, medications and allergies, an inquiry about previous sedation, anesthesia, and surgery history.

The pre-sedation assessment will allow to identify possible risks that will lead to a modification of the perioperative care in order to reduce the likelihood of adverse events and develop an appropriate sedation plan [6–9].

The pre-sedation assessment should be focused on risk identification, risk stratification, risk modification (where possible) and residual risk communication, expressed as an appropriate risk management plan [7].

Many sedation guidelines reference the American Society of Anesthesiologists (ASA) physical status classification system as a basis for risk stratification, however the ASA score, which was initially devised exclusively for adult patients, was never intended as a risk predictor, and there is increasing evidence that scoring using the ASA classification within and between disciplines can be inconsistent [10–12,108].

The ASA physical status classification system was devised in order to offer clinicians a simple categorization of a patient's physiological status and allows to divide patients into 5 classes from ASA1 being the normal healthy patient, to ASA5 being a moribund patient who is not expected to survive without the operation. A further level was added later on, the ASA6, which corresponds to a brain-dead patient whose organs are being removed for donor purposes [109,110].

The ASA classification on its own is however not a predictor of operative risk, and a careful pre-sedation assessment remains fundamental.

Rather than age or ASA status, some guidelines use red flags (e.g., for increased risk of failed sedation, risk for airway obstruction, risk of failure to provide effective manual ventilation or for other adverse outcomes) as a prompt for clinicians to consider referral to different providers [111].

Some red flags for potential complications during PSA, which should be identified during the pre-sedation assessment, include risk factors such as trauma, decreased level of consciousness, extreme obesity (BMI >95% for age and sex), pregnancy, or bowel motility dysfunction. (Table 2)

In these cases, a careful evaluation should be carried out before the administration of sedatives, and preference should be given to a lighter level of sedation or the administration of agents with less risk of depressing protective airway reflexes.

Table 2.

Red Flags for increased risk during PSA
- Severe comorbidities
- Trauma
- Decreased level of consciousness
- Pregnancy
- Obesity
- Bowel motility disfunction
- Recent alcohol consumption
- Recent substance use
- Potential difficult ventilation, or airway management

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One of the main worries when performing PSA include the need to reduce the probability of pulmonary aspiration of gastric contents. The depression of upper-airway reflexes which occurs during anesthesia is indeed a major risk factor for the development of aspiration pneumonia.

The level of sedation that one aims for during PSA is generally moderate to deep sedation, therefore the majority of patients maintain respiratory effort and protection of airway reflexes at these depths of sedation [112]. However, shifting to deeper levels of sedation may occur with some patients.

Pre-procedural fasting cannot be considered routinely applicable in the ED. The American College of Emergency Physicians (ACEP) does not consider recent food intake as a contraindication for PSA in the ED [8]. Previous studies, which studied the incidence of aspiration during ED PSA, concluded that routine fasting is not mandatory previous to procedural sedation and analgesia in the emergency department [15,113]. There is therefore no clear evidence that non-compliance with elective fasting guidance increases the risk of aspiration or other adverse events during procedural sedation in the Emergency Department. Nonetheless, Emergency clinicians should always weight the possible risks of sedating nonfasted patients with the benefits of and necessity for completing the procedure.

The clinician should therefore undertake a risk assessment taking into account dynamic risk factors for aspiration (such as alcohol ingestion), established risk factors (such as obesity, pregnancy, known bowel dysfunctions), the proposed sedation agent, and the procedure to be performed [114].

Another critical sedation-related risk is failure to maintain a patent airway and the need to support or assist inadequate spontaneous ventilation, particularly when there is inadvertent transition towards deeper levels of sedation and unconsciousness [115]. The pre-sedation assessment should therefore focus on specific ways to predict airway and breathing-related risks.

Different risk factors have been identified as predictors of a difficult airways.

A study published in 2000, observed an incidence of difficult mask ventilation (DMV) in 5% of the patients in a general adult population. This study also recognized five criteria as independent factors for a DMV (age older than 55 yr, body mass index > 26 kg/m2, beard, lack of teeth, history of snoring), and the presence of two of these risk factors indicated a high likelihood of DMV (sensitivity, 0.72; specificity, 0.73) [116].

Another study evidenced that DMV is more common in obese patients and predictors for a difficult mask ventilation include reduced mandibular protrusion, higher Mallampati score [117] and greater neck circumference [118].

Another useful tool to predict difficult airways is the DIFFMASK score, proposed by Lundstrøm et al., which allows to predict difficult facemask ventilation during general anesthesia using ten independent criteria (sex, age, BMI, history of previous difficult tracheal intubation, thyromental distance, Mallampati score, presence of beard, history of sleep apnea or snoring, and neck radiation changes) [119].

The clinician performing PSA should be able to rescue a patient who becomes inadvertently over-sedated and, where necessary, maintain an airway and establish satisfactory ventilation and oxygenation through alternative supportive oxygenation and ventilation techniques should tracheal intubation fail, and bag mask ventilation prove difficult or impossible.

3.1. Monitoring

Respiratory depression and hemodynamic instability are considered the most common and important adverse events of PSA.

PSA providers must therefore be well trained in recognizing and treating life threatening complications that may arise during sedation, and should be proficient in antidote administration (i.e., flumazenil, naloxone), advanced airway management, IV cannulation and cardiac arrest management (Advanced Life Support) [8,15] Advanced airway equipment, resuscitative medications and vascular access supplies should be easily accessible when performing PSA.

The main risks for complications linked with moderate sedation and analgesia are dependent on the drugs used, which may lead to problems on the cardiovascular or respiratory systems. These

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complications may be prevented when detected and treated in a timely manner, this is why monitoring is of fundamental importance during procedural sedation and analgesia.

Patient monitoring should include:

- monitoring of ventilation, oxygenation and gas exchanges;

This is usually assessed through clinical signs, capnography, and pulse oximetry.

Expired carbon dioxide monitoring is valuable to diagnose the simple presence or absence of respirations, airway obstruction, or respiratory depression.

Multiple studies showed that the use of continuous end-tidal carbon dioxide monitoring (i.e., capnography) is associated with a reduced frequency of hypoxemic events when compared to monitoring without capnography, so end-tidal carbon dioxide (ETCO2) monitoring has been demonstrated to be useful in the early recognition of hypoventilation and providing advanced warning of hypoxic events [8,9,120–124]. In patients receiving supplemental oxygen, capnography facilitates the recognition of apnea or airway obstruction several minutes before the situation would be detected just by pulse oximetry [14,15]. Abnormalities in capnography, however, are frequently transient and have not been shown to be related to adverse outcome or the requirement for intervention, and it is important to note that the exact value of expired carbon dioxide is less important than simple assessment of continuous respiratory gas exchange.

In 2012, the Royal College of Anaesthetists and the College of Emergency Medicine published new guidelines in the UK, which included a recommendation for the routine use of ETCO2 monitoring on all patients undergoing procedural sedation in the ED [2].

Capnography should be available for minimal and moderate sedation and is strongly advised for moderate sedation in both adults and children, and in ASA 3 or ASA 4 patients [1].

Oxygen supplementation in both moderate and severe sedation can be useful in order to prevent any possible adverse effect. The use of oxygen during procedural sedation is encouraged especially for at risk patient groups (e.g., ischaemic heart disease) and those undergoing deep sedation procedures (increased risk of short periods of apnea) [114]. Previous guidelines express a consensus on the possibility to administer supplemental oxygen during moderate procedural sedation/analgesia unless specifically contraindicated for a particular patient or procedure [8,125].

It is however important to note that, 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 [126].

- monitoring of the cardiovascular system;

This is usually assessed through repeated non-invasive measures of blood pressure (5 minutes interval), and a continuous monitoring of heart rate; continuous electrocardiographic monitoring may be useful when performing moderate sedation in patients with clinically significant cardiovascular disease or those who are undergoing procedures where dysrhythmias are anticipated.

- monitoring of the patient's level of consciousness.

This is usually monitored during PSA by clinical observation, which is performed by judging a sedated patient's response to increasing levels of stimulation [127]. Monitoring of the depth of sedation, typically by assessing the patient's response to verbal commands or stimulation, will allow to detect whether the patient is experiencing a deeper than intended sedation. Loss of patient response to stimulation or verbal commands indicates that loss of airway reflexes, respiratory and/or cardiovascular depression are likely, and sedation should be lightened accordingly.

As the risk of adverse events increases with the depth of sedation induced, frequent monitoring of level of consciousness is recommended. The most frequently cited scales for sedation and responsiveness monitoring are the Observer's Assessment of Alertness/Sedation Scale, the Richmond Agitation-Sedation Scale and the Ramsay Sedation Scale [128,129].

Monitoring of verbal response may be difficult in some special populations, for example, small children, patients with intellectual disabilities or language difficulties. Devices for the monitoring of the depth of anesthesia (like the processed electroencephalogram-based depth of anesthesia monitoring devices) provide an alternative method to monitor level of consciousness that can be used in addition to clinical observation. Research suggests that depth-of-anesthesia monitors may reduce

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intraoperative awareness and may predict anesthesia outcomes in specific high-risk populations and should be used as the main form of sedation assessment in adult patients who are in deep levels of sedations and for which subjective sedation assessments are unobtainable in these patients. Supplemental technologies to monitor the depth of sedation are however not currently advised for procedural sedation and analgesia in the setting of the Emergency Department when clinical observation can allow appreciation of the depth of sedation [130–132].

Following procedural sedation and analgesia, monitoring should be continued until the patient has reached back a baseline level of consciousness and is no longer at risk for compromission of airway patency and cardiorespiratory depression [8].

4. Special Populations Considerations

Higher-risk age groups for procedural sedation and analgesia include both pediatric patients and elderly patients (Table 3).

Emergency physicians must recognize these higher risk patients and proceed with sedation only if their level of expertise and experience justifies doing so.

Table 3. Specificity of the geriatric and pediatric populations.

The elderly patient	The pediatric patient
Risk factors: - comorbidities - polymedication - increased sensitivity to sedatives - limited physiological reserve	**Risk factors:** - uncooperative behavior - different anatomy - slower drug clearance - limited physiological reserve
Possible complications: - cardiovascular or respiratory disfunction - drug interactions - deeper than intended sedation	**Possible complications:** - deeper than intended sedation - drug-induced loss of airway patency - difficult airway management
Precautions: - pre-sedation assessment - pre-oxygenation - smaller boluses - increased redosing interval - proper monitoring	**Precautions**: - pre-sedation assessment -assessing cognitive and developmental status of the patient - airway assessment - availability of proper equipment adapted to pediatric patients.

4.1. Geriatric Population

Elderly patients are more likely to be at risk from sedation given that they often have many have co-morbidities, increased sensitivity to sedatives, and limited physiological reserve.

Elderly patients are more at risk during procedural sedation and analgesia because they are more prone to cardiorespiratory decompensation when given sedative or analgesic drugs.

The elderlies are usually more sensitive to many drugs than younger patients, and generally require lower milligram-per-kilogram doses to reach the same depth of sedation of younger patients. Elderly patients have an increased variability of drug response and decreased requirements for most anesthetic drugs. Elderly patients have an increased redosing interval, cautious administration of sedation will help reduce the risks associated with sedation in the elderly.

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When performing procedural sedation in the elderly patient, due care needs to be exercised in relation to drug choice, dosage and interactions (analgesics, sedatives and patient's regular medications) as well as the need to take into account the often-delayed onset time for sedation agents in this group. This group of patients are much more likely to have co-morbidities which impact their respiratory and cardiovascular functional reserves and these factors, as well as the patient's regular medications, need to be considered during PS decision making; especially when considering fluid and oxygen supplementation [114].

When investigating whether the elderlies (>75y.o) actually constitute a high-risk population, a prevalence of adverse events of 2.6% in the population studied was detected, without adverse outcomes. The main adverse events were respiratory complications (hypoxemia, apnea) and cardiovascular problems, such as hypotension [45]. According to these results, prevention of adverse events in the elderly may include the administration of a smaller drug boluses, as well as quality pre-oxygenation which could help protecting most apneic patients from hypoxemia.

When taking the appropriate precautions adjusted for the age of the population, several further studies had different findings for what concerns the relationship between increased age and increased risk of adverse events (mainly linked to respiratory and cardiovascular events), with studies failing to demonstrate a statistically significant incidence of complication rates in patients of at least 65 years of age when corrected doses of sedatives are administered [9,133,134].

In summary, important precautions to be adopted in the geriatric population include: a careful pre-sedation assessment taking into consideration possible drug interactions and notable comorbidities, the administration of smaller doses of sedatives with an increased redosing interval, proper monitoring, and preoxygenation to avoid hypoxemia in case of apnea.

4.2. Pediatric Population

Sedation in children is often administered to relieve pain and anxiety as well as to modify behavior (eg, immobility) to allow the safe completion of a procedure. A child's ability to control his or her own behavior to cooperate for a procedure depends both on his or her chronologic age and cognitive/emotional development.

Patients of the pediatric population possess physiological and anatomical considerations that demand supplementary knowledge and skills.

Infants and children under 6 months of age are at higher risk from sedation procedures because of slower drug clearance, decreased protein binding, increased drug passage across the blood brain barrier, and a lower ratio of lean to total body mass [135,136].

Children under 6 years of age are not only at higher risk for sedation-related adverse events than an older cohort due to the sedating medications' effect on the respiratory drive, airway patency and protective airway reflexes [137,138], but because they are less mature, and less cooperative, this group is also more at risk of deeper than intended sedation [1,139–141].

The pre-sedation risk assessment should, in addition to the items already covered for the adult population, include any history of comorbidities, congenital anomalies and malformations, which could pose a risk for airway management and the cardiovascular stability, and consideration should be given to the preparation of parents and family to the sedation/analgesia.

It is also important to identify children which could be at higher risk of laryngospasm, or children at risk of airway obstruction (in the case of obstructive sleep apnea or sleep disordered breathing), and syndromes associated with airway difficulties [1]. A focused airway examination for large and potentially obstructive tonsils (most common 2-6 years) or anatomic airway abnormalities that might increase the potential for airway obstruction, is of foremost importance to ensure the safety of the procedure.

As the American Society of Anesthesiologists (ASA) physical status classification system was devised for adult patients, the NICE guidelines have been created for pediatric patients [142].

According to NICE guidelines, pediatric patients of corresponding ASA grade 3 and above and infants (including neonates) are at greater risk for complications during sedation, and therefore the advice of a specialist should be sought when considering PSA in this special population [125].

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Similarly to the adult population, guidelines for pediatric PSA agree on the fact that procedural sedation may be safely administered to pediatric patients in the ED who have had recent oral intake [143,144]. Once again, the risk benefit ratio of performing PSA in non-fasted patients should also be weighted before starting the procedure.

No additional monitoring equipment is specifically required in the pediatric population. Capnography should be considered for all pediatric patients undergoing PSA as it may allow to detect hypoventilation and apnea earlier than pulse oximetry and/or clinical assessment alone [14,15]. This might be especially useful in the pediatric population which may not have the same respiratory reserve as the adult population and in which deterioration may occur more rapidly.

Practitioners performing PSA in the pediatric population must be able to recognize the various levels of sedation and have the skills and age- and size-appropriate equipment necessary to provide appropriate cardiopulmonary support if needed.

In summary, important precautions to be adopted in the pediatric population include: a careful pre-sedation assessment taking into consideration the psychological and developmental status of the patient as well as conditions which put more at risk the infant for a difficult airway, the choice of drug and its dose based on the age of the patient, the availability of proper equipment adapted to pediatric patients. Moreover, when considering PSA in the emergency Department for children younger than 6 months old, and children with corresponding ASA scores higher than 2, specialist advice and assistance is needed.

5. Collaboration in Procedural Sedation and Analgesia

As the fields of application of procedural sedation continue to expand, it becomes extremely evident the imperative of a mandatory collaboration and adequate training of all practitioners, regardless of their educational background. In accordance with the latest guidelines promulgated by the American Society of Anesthesiologists in 2018 [8], the need for a multidisciplinary teamwork focused on patient evaluation, preparation, monitoring, and recovery support is crucial for the successful implementation of a high-quality sedation process.

However, the goal of a tailored procedural sedation adequate for the needs of the patient still remains far from the current reality: concerns over the safety of sedation procedures keep emerging, highlighting the absence of a standardized curriculum. Many of the complications that emerged in past surveys [145,146] were mostly related to adverse drug responses, in particular in pediatric sedation [147], for which the spectrum of available drugs is extremely narrow: the majority of adverse response's complications could be avoided if detected and treated in a timely manner. That is only achievable with the presence of an individual responsible for the patient's monitoring.

Therefore, cooperation among different healthcare specialists who received formal training is imperative for optimal outcomes. Recent reviews spanning nursing [148], anesthesiology, emergency medicine [149], and pediatric emergency medicine underscore the necessity of a multidisciplinary standard in procedural sedation, especially for those procedures conducted outside of the operating room [147]. Thus, the escalating demand for such procedures driven by the increased utilization of diagnostic tools and procedural treatment methods requires a new approach to specialist training [150].

A crucial step to decrease sedation-related adverse events includes a globally unified approach and precise decision-making criteria for involving an anesthesiologist. Sedation is nowadays used for an ample range of procedures in various specialties, many of which are performed by non-anesthesiologists, such as dental care, cardiology, gastroenterology [151], emergency medicine. The techniques used in these different fields are effective for most of the patients, however, the limitations of setting, comorbidities, advanced/multiple drug use suggest the absolute need of a specialized and adequately trained individual responsible for monitoring the patient [152].

As the depth of sedation increases, the essential requirement of a strict monitoring follows: according to the previous cited Guidelines of the American Society of Anesthesiologists [8], the recommendations for patient evaluation consider monitoring of the level of consciousness, of

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respiratory and ventilation, of hemodynamic functions and the contemporaneous recording of multiple parameters.

Many hospitals and institutions have decided for a more conservative attitude towards the implementation of procedural sedation practice to minimize the perceived risk [149]. However, sedation-related events, especially airway events, are common but rarely result in an adverse outcome. Elderly patients, deeply sedated with short-acting agents, are particularly at risk [134]. Understanding mechanisms of actions of sedatives will remain crucial, alongside a global data contribution for developing a unified and targeted sedation practice [153].

Moreover, emphasis should be placed on shared decision-making between specialists and patients to determine the intervention of an anesthesiologist for high-risk patients. The provision of a patient advice leaflet [154] describing the procedure and informing both the patient and their caregivers has proven to be a valuable communication tool.

6. Future Perspectives in Procedural Sedation and Analgesia

As the demand for minimally invasive interventions continues to rise, the future of PSA is unfolding with unprecedented opportunities and challenges. The advancements made in development of novel drugs such as remimazolam and the introduction of innovative monitoring technologies, such as capnography, is bringing forth a paradigm shift in the domain of Procedural Sedation, emphasizing the need of an international discussion on the future of its training and certification, particularly in the case of non-planned situations.

In the realm of emerging drugs, remimazolam emerges as a potential game-changer in PSA practices. Its distinct pharmacokinetic profile and rapid onset of action present a promising alternative to traditional sedatives, aiming to optimize patient experience and procedural efficiency. Recent clinical trials and findings shed light on this benzodiazepine's efficacy and safety in diverse procedural settings, igniting discourse on its integration into standard PSA protocols. It distinguishes itself from other intravenous hypnotic agents, like propofol, due to its minimal propensity for causing cardiovascular depression, respiratory depression, and injection pain [155], in line with other benzodiazepines' adverse effects. The benzodiazepine antagonist flumazenil could be used to treat adverse events [106,155], not only reverting the effects of remimazolam but also contributing to expedited recovery times.

Most of remimazolam's clinical trials in procedural sedation, primarily performed in colonoscopy, upper gastrointestinal endoscopy, and bronchoscopy settings (a single report of a trial in hysteroscopy is present) demonstrate how in 70% of the procedures an adequate level of sedation was achieved with a rapid onset and offset of sedation [106]. Given its efficacy profile, it emerges as a potentially valuable drug for high risk patients, thanks to its low impact on cardiovascular and respiratory systems [106]. Moreover, remimazolam does not require dose adjustments in subjects with hepatic or renal impairment [156]. The effect of higher concomitant doses of fentanyl with remimazolam is still unclear [155].

Within the sphere of advancements in monitoring technologies for Procedural Sedation and Analgesia, real-time monitoring has become a cornerstone in ensuring heightened precision and safety during sedation procedures. Cutting-edge technologies, including advanced sedation monitors and capnography, play pivotal roles in constantly assessing patient vitals and sedation depth. As we navigate through this technological frontier, the integration of improved monitoring not only enhances patient outcomes but also reshapes the very fabric of PSA practices. According to recent reviews and trials, the incidence of composite adverse events was reduced with the addition of capnography monitoring: this was mostly due to the significant reduction of mild and severe oxygen desaturation events, which may have helped to avoid the need for assisted ventilation [157,158]. Capnography use, nonetheless, did not associate with shorter recovery time in the ED [159].

Delving into the prospect of personalized medicine within the domain of Procedural Sedation and Analgesia opens a new dimension to patient care. The concept revolves around tailoring sedation approaches based on individual patient characteristics, acknowledging the inherent variability in responses to sedative agents. Genetic factors, medical history, and other patient-specific variables

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play integral roles in influencing the efficacy and safety of sedation. This personalized approach seeks to move beyond the one-size-fits-all paradigm, aiming to optimize sedation outcomes by aligning pharmacological interventions with the unique biological makeup of each patient. Ongoing research and developments in personalized medicine offer glimpses into a future where PSA practices are finely tuned to accommodate the diversity of patient profiles and settings [14].

In this evolving landscape regarding Procedural Sedation practice, the necessity for healthcare professionals to keep up with these innovations becomes evident. Training programs need to be recalibrated in order to incorporate the nuances of administering new drugs and implement advanced monitoring tools effectively.

It emerges, from recent surveys and reviews [160,161], the absence of a clearly defined training pathway in all the medical specialties that should be able to manage PSA and its possible complications: all practitioners are required to be able to manage a scenario corresponding to two levels of sedation deeper than the programmed one for the procedure, in order to buffer for unexpected complications. While anesthesiologists and nurse anesthetists administer anesthesia within the boundaries of the operating room, practitioners offering sedation beyond the OR setting, such as those in emergency medicine, may find a suitably trained Physician's Assistant (PA) to be a cost-effective alternative for the majority of simple procedural sedation instances, allowing anesthesiologists and intensivists to focus their expertise on patients with more demanding medical needs.

The integration of critical incidence simulation in training regimens further enhances the preparedness of healthcare providers by offering realistic scenarios for refining skills in a controlled environment [161]. Simultaneously, considerations for adapting certification requirements emphasize the need for healthcare professionals to demonstrate proficiency in the application of these novel interventions.

7. Conclusions

In conclusion, the comprehensive examination of procedural sedation and analgesia (PSA) within the emergency department (ED) underscores the critical importance of this practice in facilitating a wide range of medical procedures by minimizing patient discomfort and enhancing the overall quality of care. The manuscript has highlighted the nuanced pharmacological landscape of PSA, detailing the selection, application, and potential complications associated with key sedative and analgesic agents including propofol, ketamine, dexmedetomidine, fentanyl, midazolam, etomidate, nitrous oxide, and the novel agent remimazolam. Special attention was given to the tailored approaches required for managing pediatric and geriatric populations, acknowledging their unique physiological and pharmacological considerations.

The findings reinforce the necessity of an individualized approach to PSA, rooted in a thorough pre-procedural assessment, vigilant monitoring, and readiness to address complications. This approach ensures patient safety while achieving the desired sedative and analgesic effects. Furthermore, the manuscript underscores the dynamic nature of PSA practice, driven by ongoing research and the integration of new pharmacological agents, which promise to enhance sedation safety and efficacy.

Emerging from this review is a clear mandate for emergency medicine practitioners to stay abreast of current guidelines, evidence-based practices, and advances in pharmacology. Continuous education and skill development are imperative for integrating new knowledge into clinical protocols, thereby advancing PSA practices in the ED.

Ultimately, this work advocates for the judicious application of procedural sedation and analgesia as a cornerstone of patient-centered care in emergency settings. By embracing evidence-based strategies, emergency practitioners can improve patient outcomes, reduce the psychological impact of emergency procedures, and uphold the highest standards of care in the fast-paced ED environment.

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References

1. PG09(G)-Guideline-on-Sedation-and-or-Analgesia-for-Diagnostic-and-Interventional-Medical,-Dental-or-Surgical-Procedures-(PS09).Pdf.
2. Safe_Sedation_in_the_Emergency_Department_Report_and_Recommendations.Pdf.
3. Innes, G.; Murphy, M.; Nijssen–Jordan, C.; Ducharme, J.; Drummond, A. Procedural Sedation and Analgesia in the Emergency Department. Canadian Consensus Guidelines. *The Journal of Emergency Medicine* **1999**, *17*, 145–156, doi:10.1016/S0736-4679(98)00135-8.
4. Godwin, S.A.; Caro, D.A.; Wolf, S.J.; Jagoda, A.S.; Charles, R.; Marett, B.E.; Moore, J.; American College of Emergency Physicians Clinical Policy: Procedural Sedation and Analgesia in the Emergency Department. *Ann Emerg Med* **2005**, *45*, 177–196, doi:10.1016/j.annemergmed.2004.11.002.
5. Committee of Origin: Quality Management and Departmental Administration Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia. **2009**.
6. Raffay, V.; Fišer, Z.; Samara, E.; Magounaki, K.; Chatzis, D.; Mavrovounis, G.; Mermiri, M.; Žunić, F.; Pantazopoulos, I. Challenges in Procedural Sedation and Analgesia in the Emergency Department. *Journal of Emergency and Critical Care Medicine* **2020**, *4*, doi:10.21037/jeccm-19-212.
7. Sutherland, J.R.; Conway, A.; Sanderson, E.L. Preprocedural Assessment for Patients Anticipating Sedation. *Curr Anesthesiol Rep* **2020**, *10*, 35–42, doi:10.1007/s40140-020-00368-8.
8. Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018: A Report by the American Society of Anesthesiologists Task Force on Moderate Procedural Sedation and Analgesia, the American Association of Oral and Maxillofacial Surgeons, American College of Radiology, American Dental Association, American Society of Dentist Anesthesiologists, and Society of Interventional Radiology*. *Anesthesiology* **2018**, *128*, 437–479, doi:10.1097/ALN.0000000000002043.
9. Jacques, K.G.; Dewar, A.; Gray, A.; Kerslake, D.; Leal, A.; Lees, F. Procedural Sedation and Analgesia in a Large UK Emergency Department: Factors Associated with Complications. *Emerg Med J* **2011**, *28*, 1036–1040, doi:10.1136/emj.2010.102475.
10. Mak, P.H.K.; Campbell, R.C.H.; Irwin, M.G.; American Society of Anesthesiologists The ASA Physical Status Classification: Inter-Observer Consistency. American Society of Anesthesiologists. *Anaesth Intensive Care* **2002**, *30*, 633–640, doi:10.1177/0310057X0203000516.
11. Clough, S.; Shehabi, Z.; Morgan, C. Medical Risk Assessment in Dentistry: Use of the American Society of Anesthesiologists Physical Status Classification. *Br Dent J* **2016**, *220*, 103–108, doi:10.1038/sj.bdj.2016.87.
12. Theivanayagam, S.; Lopez, K.T.; Matteson-Kome, M.L.; Bechtold, M.L.; Asombang, A.W. ASA Classification Pre-Endoscopic Procedures: A Retrospective Analysis on the Accuracy of Gastroenterologists. *South Med J* **2017**, *110*, 79–82, doi:10.14423/SMJ.0000000000000610.
13. Sneyd, J.R.; Rigby-Jones, A.E. Remimazolam for Anaesthesia or Sedation. *Curr Opin Anaesthesiol* **2020**, *33*, 506–511, doi:10.1097/ACO.0000000000000877.
14. Coté, C.J.; Wilson, S.; AMERICAN ACADEMY OF PEDIATRICS; AMERICAN ACADEMY OF PEDIATRIC DENTISTRY Guidelines for Monitoring and Management of Pediatric Patients Before, During, and After Sedation for Diagnostic and Therapeutic Procedures. *Pediatrics* **2019**, *143*, e20191000, doi:10.1542/peds.2019-1000.

15. Godwin, S.A.; Burton, J.H.; Gerardo, C.J.; Hatten, B.W.; Mace, S.E.; Silvers, S.M.; Fesmire, F.M. Clinical Policy: Procedural Sedation and Analgesia in the Emergency Department. *Annals of Emergency Medicine* **2014**, *63*, 247-258.e18, doi:10.1016/j.annemergmed.2013.10.015.
16. Bellolio, M.F.; Gilani, W.I.; Barrionuevo, P.; Murad, M.H.; Erwin, P.J.; Anderson, J.R.; Miner, J.R.; Hess, E.P. Incidence of Adverse Events in Adults Undergoing Procedural Sedation in the Emergency Department: A Systematic Review and Meta-Analysis. *Acad Emerg Med* **2016**, *23*, 119–134, doi:10.1111/acem.12875.
17. Gan, T.J. Pharmacokinetic and Pharmacodynamic Characteristics of Medications Used for Moderate Sedation. *Clin Pharmacokinet* **2006**, *45*, 855–869, doi:10.2165/00003088-200645090-00001.
18. Hansen, T.G. Sedative Medications Outside the Operating Room and the Pharmacology of Sedatives. *Curr Opin Anaesthesiol* **2015**, *28*, 446–452, doi:10.1097/ACO.0000000000000202.
19. Yoo, H.; Iirola, T.; Vilo, S.; Manner, T.; Aantaa, R.; Lahtinen, M.; Scheinin, M.; Olkkola, K.T.; Jusko, W.J. Mechanism-Based Population Pharmacokinetic and Pharmacodynamic Modeling of Intravenous and Intranasal Dexmedetomidine in Healthy Subjects. *Eur J Clin Pharmacol* **2015**, *71*, 1197–1207, doi:10.1007/s00228-015-1913-0.
20. Hinkelbein, J.; Lamperti, M.; Akeson, J.; Santos, J.; Costa, J.; De Robertis, E.; Longrois, D.; Novak-Jankovic, V.; Petrini, F.; Struys, M.M.R.F.; et al. European Society of Anaesthesiology and European Board of Anaesthesiology Guidelines for Procedural Sedation and Analgesia in Adults. *Eur J Anaesthesiol* **2018**, *35*, 6–24, doi:10.1097/EJA.0000000000000683.
21. Homma, Y.; Norii, T.; Kanazawa, T.; Hoshino, A.; Arino, S.; Takase, H.; Albright, D.; Funakoshi, H.; Japan Society of Procedural Sedation and Analgesia A Mini-Review of Procedural Sedation and Analgesia in the Emergency Department. *Acute Med Surg* **2020**, *7*, e574, doi:10.1002/ams2.574.
22. Miner, J.R.; Burton, J.H. Clinical Practice Advisory: Emergency Department Procedural Sedation with Propofol. *Ann Emerg Med* **2007**, *50*, 182–187, 187.e1, doi:10.1016/j.annemergmed.2006.12.017.
23. Ghojazadeh, M.; Sanaie, S.; Paknezhad, S.P.; Faghih, S.-S.; Soleimanpour, H. Using Ketamine and Propofol for Procedural Sedation of Adults in the Emergency Department: A Systematic Review and Meta-Analysis. *Adv Pharm Bull* **2019**, *9*, 5–11, doi:10.15171/apb.2019.002.
24. Soleimanpour, H.; Taheraghdam, A.; Ghafouri, R.R.; Taghizadieh, A.; Marjany, K.; Soleimanpour, M. Improvement of Refractory Migraine Headache by Propofol: Case Series. *Int J Emerg Med* **2012**, *5*, 19, doi:10.1186/1865-1380-5-19.
25. Sellgren, J.; Ejnell, H.; Elam, M.; Pontén, J.; Wallin, B.G. Sympathetic Muscle Nerve Activity, Peripheral Blood Flows, and Baroreceptor Reflexes in Humans during Propofol Anesthesia and Surgery. *Anesthesiology* **1994**, *80*, 534–544, doi:10.1097/00000542-199403000-00009.
26. Petros, A.J.; Bogle, R.G.; Pearson, J.D. Propofol Stimulates Nitric Oxide Release from Cultured Porcine Aortic Endothelial Cells. *Br J Pharmacol* **1993**, *109*, 6–7, doi:10.1111/j.1476-5381.1993.tb13523.x.
27. Bryson, H.M.; Fulton, B.R.; Faulds, D. Propofol. An Update of Its Use in Anaesthesia and Conscious Sedation. *Drugs* **1995**, *50*, 513–559, doi:10.2165/00003495-199550030-00008.
28. Raoof, A.A.; Augustijns, P.F.; Verbeeck, R.K. In Vivo Assessment of Intestinal, Hepatic, and Pulmonary First Pass Metabolism of Propofol in the Rat. *Pharm Res* **1996**, *13*, 891–895, doi:10.1023/a:1016057229478.
29. Hughes, M.A.; Glass, P.S.; Jacobs, J.R. Context-Sensitive Half-Time in Multicompartment Pharmacokinetic Models for Intravenous Anesthetic Drugs. *Anesthesiology* **1992**, *76*, 334–341, doi:10.1097/00000542-199203000-00003.
30. Sahinovic, M.M.; Struys, M.M.R.F.; Absalom, A.R. Clinical Pharmacokinetics and Pharmacodynamics of Propofol. *Clin Pharmacokinet* **2018**, *57*, 1539–1558, doi:10.1007/s40262-018-0672-3.
31. Hiraoka, H.; Yamamoto, K.; Miyoshi, S.; Morita, T.; Nakamura, K.; Kadoi, Y.; Kunimoto, F.; Horiuchi, R. Kidneys Contribute to the Extrahepatic Clearance of Propofol in Humans, but Not Lungs and Brain. *Br J Clin Pharmacol* **2005**, *60*, 176–182, doi:10.1111/j.1365-2125.2005.02393.x.
32. Rudolph, U.; Antkowiak, B. Molecular and Neuronal Substrates for General Anaesthetics. *Nat Rev Neurosci* **2004**, *5*, 709–720, doi:10.1038/nrn1496.
33. Matsuo, M.; Ayuse, T.; Oi, K.; Kataoka, Y. Propofol Produces Anticonflict Action by Inhibiting 5-HT Release in Rat Dorsal Hippocampus. *Neuroreport* **1997**, *8*, 3087–3090, doi:10.1097/00001756-199709290-00016.
34. Cavazzuti, M.; Porro, C.A.; Barbieri, A.; Galetti, A. Brain and Spinal Cord Metabolic Activity during Propofol Anaesthesia. *Br J Anaesth* **1991**, *66*, 490–495, doi:10.1093/bja/66.4.490.
35. Strebel, S.; Lam, A.M.; Matta, B.; Mayberg, T.S.; Aaslid, R.; Newell, D.W. Dynamic and Static Cerebral Autoregulation during Isoflurane, Desflurane, and Propofol Anesthesia. *Anesthesiology* **1995**, *83*, 66–76, doi:10.1097/00000542-199507000-00008.
36. Ebert, T.J. Sympathetic and Hemodynamic Effects of Moderate and Deep Sedation with Propofol in Humans. *Anesthesiology* **2005**, *103*, 20–24, doi:10.1097/00000542-200507000-00007.
37. Nieuwenhuijs, D.; Sarton, E.; Teppema, L.; Dahan, A. Propofol for Monitored Anesthesia Care: Implications on Hypoxic Control of Cardiorespiratory Responses. *Anesthesiology* **2000**, *92*, 46–54, doi:10.1097/00000542-200001000-00013.

38. Nieuwenhuijs, D.; Sarton, E.; Teppema, L.J.; Kruyt, E.; Olievier, I.; van Kleef, J.; Dahan, A. Respiratory Sites of Action of Propofol: Absence of Depression of Peripheral Chemoreflex Loop by Low-Dose Propofol. *Anesthesiology* **2001**, *95*, 889–895, doi:10.1097/00000542-200110000-00017.
39. McKeating, K.; Bali, I.M.; Dundee, J.W. The Effects of Thiopentone and Propofol on Upper Airway Integrity. *Anaesthesia* **1988**, *43*, 638–640, doi:10.1111/j.1365-2044.1988.tb04146.x.
40. Aboian, M.; Johnson, J.M.; Ginat, D.T. Propofol. In *Neuroimaging Pharmacopoeia*; Springer International Publishing, 2015; pp. 347–349 ISBN 978-3-319-12714-9.
41. Miller, K.A.; Andolfatto, G.; Miner, J.R.; Burton, J.H.; Krauss, B.S. Clinical Practice Guideline for Emergency Department Procedural Sedation With Propofol: 2018 Update. *Ann Emerg Med* **2019**, *73*, 470–480, doi:10.1016/j.annemergmed.2018.12.012.
42. Diprivan (Propofol): Manufacturer's Package Insert. US National Library of Medicine.
43. Ickx, B.; Cockshott, I.D.; Barvais, L.; Byttebier, G.; De Pauw, L.; Vandesteene, A.; D'Hollander, A.A. Propofol Infusion for Induction and Maintenance of Anaesthesia in Patients with End-Stage Renal Disease. *Br J Anaesth* **1998**, *81*, 854–860, doi:10.1093/bja/81.6.854.
44. Kim, S.; Hahn, S.; Jang, M.-J.; Choi, Y.; Hong, H.; Lee, J.-H.; Kim, H.-S. Evaluation of the Safety of Using Propofol for Paediatric Procedural Sedation: A Systematic Review and Meta-Analysis. *Sci Rep* **2019**, *9*, 12245, doi:10.1038/s41598-019-48724-x.
45. Homfray, G.; Palmer, A.; Grimsmo-Powney, H.; Appelboam, A.; Lloyd, G. Procedural Sedation of Elderly Patients by Emergency Physicians: A Safety Analysis of 740 Patients. *British Journal of Anaesthesia* **2018**, *121*, 1236–1241, doi:10.1016/j.bja.2018.07.038.
46. Weaver, C.S.; Hauter, W.E.; Brizendine, E.J.; Cordell, W.H. Emergency Department Procedural Sedation with Propofol: Is It Safe? *J Emerg Med* **2007**, *33*, 355–361, doi:10.1016/j.jemermed.2007.03.014.
47. Desousa, K.A. Pain on Propofol Injection: Causes and Remedies. *Indian J Pharmacol* **2016**, *48*, 617–623, doi:10.4103/0253-7613.194845.
48. Schep, L.J.; Slaughter, R.J.; Watts, M.; Mackenzie, E.; Gee, P. The Clinical Toxicology of Ketamine. *Clin Toxicol (Phila)* **2023**, *61*, 415–428, doi:10.1080/15563650.2023.2212125.
49. Peltoniemi, M.A.; Hagelberg, N.M.; Olkkola, K.T.; Saari, T.I. Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy. *Clin Pharmacokinet* **2016**, *55*, 1059–1077, doi:10.1007/s40262-016-0383-6.
50. Rosenbaum, S.B.; Gupta, V.; Patel, P.; Palacios, J.L. Ketamine. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2024.
51. Brown, T.B.; Lovato, L.M.; Parker, D. Procedural Sedation in the Acute Care Setting. *Am Fam Physician* **2005**, *71*, 85–90.
52. Nichols, K.A.; Paciullo, C.A. Subdissociative Ketamine Use in the Emergency Department. *Adv Emerg Nurs J* **2019**, *41*, 15–22, doi:10.1097/TME.0000000000000222.
53. BinKharfi, M.; AlSagre, A. BET 2: Safety and Efficacy of Low-Dose Ketamine versus Opioids for Acute Pain Management in the ED. *Emerg Med J* **2019**, *36*, 128–129, doi:10.1136/emermed-2019-208441.2.
54. Hirota, K.; Lambert, D.G. Ketamine; History and Role in Anesthetic Pharmacology. *Neuropharmacology* **2022**, *216*, 109171, doi:10.1016/j.neuropharm.2022.109171.
55. Green, S.M.; Roback, M.G.; Kennedy, R.M.; Krauss, B. Clinical Practice Guideline for Emergency Department Ketamine Dissociative Sedation: 2011 Update. *Ann Emerg Med* **2011**, *57*, 449–461, doi:10.1016/j.annemergmed.2010.11.030.
56. Goddard, K.; Sampson, C.; Bedy, S.-M.; Ghadban, R.; Stilley, J. Effect of Ketamine on Cardiovascular Function During Procedural Sedation of Adults. *Cureus* **2021**, *13*, e14228, doi:10.7759/cureus.14228.
57. Erstad, B.L.; Barletta, J.F. Drug Dosing in the Critically Ill Obese Patient-a Focus on Sedation, Analgesia, and Delirium. *Crit Care* **2020**, *24*, 315, doi:10.1186/s13054-020-03040-z.
58. Andolfatto, G.; Abu-Laban, R.B.; Zed, P.J.; Staniforth, S.M.; Stackhouse, S.; Moadebi, S.; Willman, E. Ketamine-Propofol Combination (Ketofol) versus Propofol Alone for Emergency Department Procedural Sedation and Analgesia: A Randomized Double-Blind Trial. *Ann Emerg Med* **2012**, *59*, 504-512.e1-2, doi:10.1016/j.annemergmed.2012.01.017.
59. Strayer, R.J.; Nelson, L.S. Adverse Events Associated with Ketamine for Procedural Sedation in Adults. *Am J Emerg Med* **2008**, *26*, 985–1028, doi:10.1016/j.ajem.2007.12.005.
60. Akhlaghi, N.; Payandemehr, P.; Yaseri, M.; Akhlaghi, A.A.; Abdolrazaghnejad, A. Premedication With Midazolam or Haloperidol to Prevent Recovery Agitation in Adults Undergoing Procedural Sedation With Ketamine: A Randomized Double-Blind Clinical Trial. *Ann Emerg Med* **2019**, *73*, 462–469, doi:10.1016/j.annemergmed.2018.11.016.
61. Page, R.L.; O'Bryant, C.L.; Cheng, D.; Dow, T.J.; Ky, B.; Stein, C.M.; Spencer, A.P.; Trupp, R.J.; Lindenfeld, J.; American Heart Association Clinical Pharmacology and Heart Failure and Transplantation Committees of the Council on Clinical Cardiology; et al. Drugs That May Cause or Exacerbate Heart Failure: A Scientific Statement From the American Heart Association. *Circulation* **2016**, *134*, e32-69, doi:10.1161/CIR.0000000000000426.

62. Stefánsson, T.; Wickström, I.; Haljamäe, H. Hemodynamic and Metabolic Effects of Ketamine Anesthesia in the Geriatric Patient. *Acta Anaesthesiol Scand* **1982**, *26*, 371–377, doi:10.1111/j.1399-6576.1982.tb01785.x.
63. Arcangeli, A.; D'Alò, C.; Gaspari, R. Dexmedetomidine Use in General Anaesthesia. *Curr Drug Targets* **2009**, *10*, 687–695, doi:10.2174/138945009788982423.
64. Barends, C.R.M.; Absalom, A.; van Minnen, B.; Vissink, A.; Visser, A. Dexmedetomidine versus Midazolam in Procedural Sedation. A Systematic Review of Efficacy and Safety. *PLoS One* **2017**, *12*, e0169525, doi:10.1371/journal.pone.0169525.
65. Ghojazadeh, M.; Paknezhad, S.P.; Mohammadzadeh, S.; Vahed, N.; Rajabpour, Z.; Rezaei, M.; Soleimanpour, H. Dexmedetomidine for Procedural Sedation in the Emergency Department: A Systematic Review. *Shiraz E-Medical Journal* **2021**, *In Press*, doi:10.5812/semj.113099.
66. Bekker, A.; Sturaitis, M.K. Dexmedetomidine for Neurological Surgery. *Neurosurgery* **2005**, *57*, 1–10; discussion 1-10, doi:10.1227/01.neu.0000163476.42034.a1.
67. Vuyk, J.; Sitsen, E.; Reekers, M. Intravenous Anesthetics. **2014**, 821–863.
68. Hall, J.E.; Uhrich, T.D.; Barney, J.A.; Arain, S.R.; Ebert, T.J. Sedative, Amnestic, and Analgesic Properties of Small-Dose Dexmedetomidine Infusions. *Anesth Analg* **2000**, *90*, 699–705, doi:10.1097/00000539-200003000-00035.
69. Weerink, M.A.S.; Struys, M.M.R.F.; Hannivoort, L.N.; Barends, C.R.M.; Absalom, A.R.; Colin, P. Clinical Pharmacokinetics and Pharmacodynamics of Dexmedetomidine. *Clin Pharmacokinet* **2017**, *56*, 893–913, doi:10.1007/s40262-017-0507-7.
70. Penttilä, J.; Helminen, A.; Anttila, M.; Hinkka, S.; Scheinin, H. Cardiovascular and Parasympathetic Effects of Dexmedetomidine in Healthy Subjects. *Can J Physiol Pharmacol* **2004**, *82*, 359–362, doi:10.1139/y04-028.
71. Lee, S. Dexmedetomidine: Present and Future Directions. *Korean J Anesthesiol* **2019**, *72*, 323–330, doi:10.4097/kja.19259.
72. Tobias, J.D. Dexmedetomidine and Ketamine: An Effective Alternative for Procedural Sedation? *Pediatr Crit Care Med* **2012**, *13*, 423–427, doi:10.1097/PCC.0b013e318238b81c.
73. Lodenius, Å.; Ebberyd, A.; Hårdemark Cedborg, A.; Hagel, E.; Mkrtchian, S.; Christensson, E.; Ullman, J.; Scheinin, M.; Eriksson, L.I.; Jonsson Fagerlund, M. Sedation with Dexmedetomidine or Propofol Impairs Hypoxic Control of Breathing in Healthy Male Volunteers: A Nonblinded, Randomized Crossover Study. *Anesthesiology* **2016**, *125*, 700–715, doi:10.1097/ALN.0000000000001236.
74. Bauerschmidt, A.; Al-Bermani, T.; Ali, S.; Bass, B.; Dorilio, J.; Rosenberg, J.; Al-Mufti, F. Modern Sedation and Analgesia Strategies in Neurocritical Care. *Curr Neurol Neurosci Rep* **2023**, *23*, 149–158, doi:10.1007/s11910-023-01261-7.
75. Anttila, M.; Penttilä, J.; Helminen, A.; Vuorilehto, L.; Scheinin, H. Bioavailability of Dexmedetomidine after Extravascular Doses in Healthy Subjects. *Br J Clin Pharmacol* **2003**, *56*, 691–693, doi:10.1046/j.1365-2125.2003.01944.x.
76. Zhong, W.; Zhang, Y.; Zhang, M.-Z.; Huang, X.-H.; Li, Y.; Li, R.; Liu, Q.-W. Pharmacokinetics of Dexmedetomidine Administered to Patients with End-Stage Renal Failure and Secondary Hyperparathyroidism Undergoing General Anaesthesia. *J Clin Pharm Ther* **2018**, *43*, 414–421, doi:10.1111/jcpt.12652.
77. Benzoni, T.; Cascella, M. Procedural Sedation. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2024.
78. Reel, B.; Maani, C.V. Dexmedetomidine. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2024.
79. Stanley, T.H. The Fentanyl Story. *J Pain* **2014**, *15*, 1215–1226, doi:10.1016/j.jpain.2014.08.010.
80. Ramos-Matos, C.F.; Bistas, K.G.; Lopez-Ojeda, W. Fentanyl. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2024.
81. Scholz, J.; Steinfath, M.; Schulz, M. Clinical Pharmacokinetics of Alfentanil, Fentanyl and Sufentanil. An Update. *Clin Pharmacokinet* **1996**, *31*, 275–292, doi:10.2165/00003088-199631040-00004.
82. Kuip, E.J.M.; Zandvliet, M.L.; Koolen, S.L.W.; Mathijssen, R.H.J.; van der Rijt, C.C.D. A Review of Factors Explaining Variability in Fentanyl Pharmacokinetics; Focus on Implications for Cancer Patients. *Br J Clin Pharmacol* **2017**, *83*, 294–313, doi:10.1111/bcp.13129.
83. Bahn, E.L.; Holt, K.R. Procedural Sedation and Analgesia: A Review and New Concepts. *Emerg Med Clin North Am* **2005**, *23*, 503–517, doi:10.1016/j.emc.2004.12.013.
84. Horn, E.; Nesbit, S.A. Pharmacology and Pharmacokinetics of Sedatives and Analgesics. *Gastrointest Endosc Clin N Am* **2004**, *14*, 247–268, doi:10.1016/j.giec.2004.01.001.
85. Lingamchetty, T.N.; Hosseini, S.A.; Saadabadi, A. Midazolam. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2024.
86. Williams, L.M.; Boyd, K.L.; Fitzgerald, B.M. Etomidate. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2024.
87. Nestor, N.B.; Burton, J.H. ED Use of Etomidate for Rapid Sequence Induction. *Am J Emerg Med* **2008**, *26*, 946–950, doi:10.1016/j.ajem.2007.12.002.

88. Erdoes, G.; Basciani, R.M.; Eberle, B. Etomidate--a Review of Robust Evidence for Its Use in Various Clinical Scenarios. *Acta Anaesthesiol Scand* **2014**, *58*, 380–389, doi:10.1111/aas.12289.
89. Falk, J.; Zed, P.J. Etomidate for Procedural Sedation in the Emergency Department. *Ann Pharmacother* **2004**, *38*, 1272–1277, doi:10.1345/aph.1E008.
90. Valk, B.I.; Struys, M.M.R.F. Etomidate and Its Analogs: A Review of Pharmacokinetics and Pharmacodynamics. *Clin Pharmacokinet* **2021**, *60*, 1253–1269, doi:10.1007/s40262-021-01038-6.
91. Dumps, C.; Bolkenius, D.; Halbeck, E. [Etomidate for intravenous induction of anaesthesia]. *Anaesthesist* **2017**, *66*, 969–980, doi:10.1007/s00101-017-0381-6.
92. Miner, J.R.; Danahy, M.; Moch, A.; Biros, M. Randomized Clinical Trial of Etomidate versus Propofol for Procedural Sedation in the Emergency Department. *Ann Emerg Med* **2007**, *49*, 15–22, doi:10.1016/j.annemergmed.2006.06.042.
93. Choi, G.J.; Kang, H.; Baek, C.W.; Jung, Y.H.; Ko, J.S. Etomidate versus Propofol Sedation for Electrical External Cardioversion: A Meta-Analysis. *Curr Med Res Opin* **2018**, *34*, 2023–2029, doi:10.1080/03007995.2018.1519501.
94. Zhou, C.; Zhu, Y.; Liu, Z.; Ruan, L. Effect of Pretreatment with Midazolam on Etomidate-Induced Myoclonus: A Meta-Analysis. *J Int Med Res* **2017**, *45*, 399–406, doi:10.1177/0300060516682882.
95. Schenarts, C.L.; Burton, J.H.; Riker, R.R. Adrenocortical Dysfunction Following Etomidate Induction in Emergency Department Patients. *Acad Emerg Med* **2001**, *8*, 1–7, doi:10.1111/j.1553-2712.2001.tb00537.x.
96. Knuf, K.; Maani, C.V. Nitrous Oxide. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2024.
97. Emmanouil, D.E.; Quock, R.M. Advances in Understanding the Actions of Nitrous Oxide. *Anesth Prog* **2007**, *54*, 9–18, doi:10.2344/0003-3006(2007)54[9:AIUTAO]2.0.CO;2.
98. Galinski, M.; Hoffman, L.; Bregeaud, D.; Kamboua, M.; Ageron, F.-X.; Rouanet, C.; Hubert, J.-C.; Istria, J.; Ruscev, M.; Tazarourte, K.; et al. Procedural Sedation and Analgesia in Trauma Patients in an Out-of-Hospital Emergency Setting: A Prospective Multicenter Observational Study. *Prehosp Emerg Care* **2018**, *22*, 497–505, doi:10.1080/10903127.2017.1413464.
99. Becker, D.E.; Rosenberg, M. Nitrous Oxide and the Inhalation Anesthetics. *Anesth Prog* **2008**, *55*, 124–130; quiz 131–132, doi:10.2344/0003-3006-55.4.124.
100. Mohan, R.; Asir, V.D.; Shanmugapriyan, null; Ebenezr, V.; Dakir, A.; Balakrishnan, null; Jacob, J. Nitrousoxide as a Conscious Sedative in Minor Oral Surgical Procedure. *J Pharm Bioallied Sci* **2015**, *7*, S248-250, doi:10.4103/0975-7406.155939.
101. Swart, G.; Blair, C.; Lu, Z.; Yogendran, S.; Offord, J.; Sutherland, E.; Barnes, S.; Palavra, N.; Cremer, P.; Bolitho, S.; et al. Nitrous Oxide-Induced Myeloneuropathy. *Eur J Neurol* **2021**, *28*, 3938–3944, doi:10.1111/ene.15077.
102. Myles, P.S.; Leslie, K.; Chan, M.T.V.; Forbes, A.; Paech, M.J.; Peyton, P.; Silbert, B.S.; Pascoe, E.; ENIGMA Trial Group Avoidance of Nitrous Oxide for Patients Undergoing Major Surgery: A Randomized Controlled Trial. *Anesthesiology* **2007**, *107*, 221–231, doi:10.1097/01.anes.0000270723.30772.da.
103. Hu, Q.; Liu, X.; Wen, C.; Li, D.; Lei, X. Remimazolam: An Updated Review of a New Sedative and Anaesthetic. *Drug Des Devel Ther* **2022**, *16*, 3957–3974, doi:10.2147/DDDT.S384155.
104. Rogers, W.K.; McDowell, T.S. Remimazolam, a Short-Acting GABA(A) Receptor Agonist for Intravenous Sedation and/or Anesthesia in Day-Case Surgical and Non-Surgical Procedures. *IDrugs* **2010**, *13*, 929–937.
105. Schüttler, J.; Eisenried, A.; Lerch, M.; Fechner, J.; Jeleazcov, C.; Ihmsen, H. Pharmacokinetics and Pharmacodynamics of Remimazolam (CNS 7056) after Continuous Infusion in Healthy Male Volunteers: Part I. Pharmacokinetics and Clinical Pharmacodynamics. *Anesthesiology* **2020**, *132*, 636–651, doi:10.1097/ALN.0000000000003103.
106. Kilpatrick, G.J. Remimazolam: Non-Clinical and Clinical Profile of a New Sedative/Anesthetic Agent. *Front Pharmacol* **2021**, *12*, 690875, doi:10.3389/fphar.2021.690875.
107. Wesolowski, A.M.; Zaccagnino, M.P.; Malapero, R.J.; Kaye, A.D.; Urman, R.D. Remimazolam: Pharmacologic Considerations and Clinical Role in Anesthesiology. *Pharmacotherapy* **2016**, *36*, 1021–1027, doi:10.1002/phar.1806.
108. Mayhew, D.; Mendonca, V.; Murthy, B.V.S. A Review of ASA Physical Status - Historical Perspectives and Modern Developments. *Anaesthesia* **2019**, *74*, 373–379, doi:10.1111/anae.14569.
109. Doyle, D.J.; Hendrix, J.M.; Garmon, E.H. American Society of Anesthesiologists Classification. In *StatPearls [Internet]*; StatPearls Publishing, 2023.
110. Fitz-Henry, J. The ASA Classification and Peri-Operative Risk. *Ann R Coll Surg Engl* **2011**, *93*, 185–187, doi:10.1308/147870811X565070a.
111. Minimum Standards for Safe Procedural Sedation.Pdf.
112. Molina, J.A.D.; Lobo, C.A.; Goh, H.K.; Seow, E.; Heng, B.H. Review of Studies and Guidelines on Fasting and Procedural Sedation at the Emergency Department. *Int J Evid Based Healthc* **2010**, *8*, 75–78, doi:10.1111/j.1744-1609.2010.00163.x.
113. Thorpe, R.J.; Benger, J. Pre-Procedural Fasting in Emergency Sedation. *Emerg Med J* **2010**, *27*, 254–261, doi:10.1136/emj.2008.069120.

114. RCEM_BPC_Procedural_Sedation_Final_Aug_22.Pdf.
115. Safe_Sedation_Practice_1213.Pdf.
116. Langeron, O.; Masso, E.; Huraux, C.; Guggiari, M.; Bianchi, A.; Coriat, P.; Riou, B. Prediction of Difficult Mask Ventilation. *Anesthesiology* **2000**, *92*, 1229–1236, doi:10.1097/00000542-200005000-00009.
117. Stutz, E.W.; Rondeau, B. Mallampati Score. In *StatPearls*; StatPearls Publishing: Treasure Island (FL), 2023.
118. Leoni, A.; Arlati, S.; Ghisi, D.; Verwej, M.; Lugani, D.; Ghisi, P.; Cappelleri, G.; Cedrati, V.; El Tantawi Ali Alsheraei, A.; Pocar, M.; et al. Difficult Mask Ventilation in Obese Patients: Analysis of Predictive Factors. *Minerva Anestesiol* **2014**, *80*, 149–157.
119. Lundstrøm, L.H.; Rosenstock, C.V.; Wetterslev, J.; Nørskov, A.K. The DIFFMASK Score for Predicting Difficult Facemask Ventilation: A Cohort Study of 46,804 Patients. *Anaesthesia* **2019**, *74*, 1267–1276, doi:10.1111/anae.14701.
120. Beitz, A.; Riphaus, A.; Meining, A.; Kronshage, T.; Geist, C.; Wagenpfeil, S.; Weber, A.; Jung, A.; Bajbouj, M.; Pox, C.; et al. Capnographic Monitoring Reduces the Incidence of Arterial Oxygen Desaturation and Hypoxemia during Propofol Sedation for Colonoscopy: A Randomized, Controlled Study (ColoCap Study). *Am J Gastroenterol* **2012**, *107*, 1205–1212, doi:10.1038/ajg.2012.136.
121. Langhan, M.L.; Shabanova, V.; Li, F.-Y.; Bernstein, S.L.; Shapiro, E.D. A Randomized Controlled Trial of Capnography during Sedation in a Pediatric Emergency Setting. *Am J Emerg Med* **2015**, *33*, 25–30, doi:10.1016/j.ajem.2014.09.050.
122. Mehta, P.P.; Kochhar, G.; Albeldawi, M.; Kirsh, B.; Rizk, M.; Putka, B.; John, B.; Wang, Y.; Breslaw, N.; Lopez, R.; et al. Capnographic Monitoring in Routine EGD and Colonoscopy With Moderate Sedation: A Prospective, Randomized, Controlled Trial. *Am J Gastroenterol* **2016**, *111*, 395–404, doi:10.1038/ajg.2015.437.
123. Qadeer, M.A.; Vargo, J.J.; Dumot, J.A.; Lopez, R.; Trolli, P.A.; Stevens, T.; Parsi, M.A.; Sanaka, M.R.; Zuccaro, G. Capnographic Monitoring of Respiratory Activity Improves Safety of Sedation for Endoscopic Cholangiopancreatography and Ultrasonography. *Gastroenterology* **2009**, *136*, 1568–1576; quiz 1819–1820, doi:10.1053/j.gastro.2009.02.004.
124. Slagelse, C.; Vilmann, P.; Hornslet, P.; Jørgensen, H.L.; Horsted, T.I. The Role of Capnography in Endoscopy Patients Undergoing Nurse-Administered Propofol Sedation: A Randomized Study. *Scand J Gastroenterol* **2013**, *48*, 1222–1230, doi:10.3109/00365521.2013.830327.
125. PS09 Sedation Guidelines 2014.Pdf.
126. Maurer, W.G.; Walsh, M.; Viazis, N. Basic Requirements for Monitoring Sedated Patients: Blood Pressure, Pulse Oximetry, and EKG. *Digestion* **2010**, *82*, 87–89, doi:10.1159/000285505.
127. Sheahan, C.G.; Mathews, D.M. Monitoring and Delivery of Sedation. *Br J Anaesth* **2014**, *113 Suppl 2*, ii37-47, doi:10.1093/bja/aeu378.
128. Chernik, D.A.; Gillings, D.; Laine, H.; Hendler, J.; Silver, J.M.; Davidson, A.B.; Schwam, E.M.; Siegel, J.L. Validity and Reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with Intravenous Midazolam. *J Clin Psychopharmacol* **1990**, *10*, 244–251.
129. Frenzel, D.; Greim, C.-A.; Sommer, C.; Bauerle, K.; Roewer, N. Is the Bispectral Index Appropriate for Monitoring the Sedation Level of Mechanically Ventilated Surgical ICU Patients? *Intensive Care Med* **2002**, *28*, 178–183, doi:10.1007/s00134-001-1183-4.
130. Conway, A.; Sutherland, J. Depth of Anaesthesia Monitoring during Procedural Sedation and Analgesia: A Systematic Review and Meta-Analysis. *Int J Nurs Stud* **2016**, *63*, 201–212, doi:10.1016/j.ijnurstu.2016.05.004.
131. Fahy, B.G.; Chau, D.F. The Technology of Processed Electroencephalogram Monitoring Devices for Assessment of Depth of Anesthesia. *Anesthesia & Analgesia* **2018**, *126*, 111, doi:10.1213/ANE.0000000000002331.
132. Rasulo, F.A.; Hopkins, P.; Lobo, F.A.; Pandin, P.; Matta, B.; Carozzi, C.; Romagnoli, S.; Absalom, A.; Badenes, R.; Bleck, T.; et al. Processed Electroencephalogram-Based Monitoring to Guide Sedation in Critically Ill Adult Patients: Recommendations from an International Expert Panel-Based Consensus. *Neurocrit Care* **2023**, *38*, 296–311, doi:10.1007/s12028-022-01565-5.
133. Weaver, C.S.; Terrell, K.M.; Bassett, R.; Swiler, W.; Sandford, B.; Avery, S.; Perkins, A.J. ED Procedural Sedation of Elderly Patients: Is It Safe? *The American Journal of Emergency Medicine* **2011**, *29*, 541–544, doi:10.1016/j.ajem.2009.12.017.
134. Taylor, D.M.; Bell, A.; Holdgate, A.; MacBean, C.; Huynh, T.; Thom, O.; Augello, M.; Millar, R.; Day, R.; Williams, A.; et al. Risk Factors for Sedation-Related Events during Procedural Sedation in the Emergency Department. *Emerg Med Australas* **2011**, *23*, 466–473, doi:10.1111/j.1742-6723.2011.01419.x.
135. Ku, L.C.; Smith, P.B. Dosing in Neonates: Special Considerations in Physiology and Trial Design. *Pediatr Res* **2015**, *77*, 2–9, doi:10.1038/pr.2014.143.
136. Lu, H.; Rosenbaum, S. Developmental Pharmacokinetics in Pediatric Populations. *J Pediatr Pharmacol Ther* **2014**, *19*, 262–276, doi:10.5863/1551-6776-19.4.262.

137. Coté, C.J.; Karl, H.W.; Notterman, D.A.; Weinberg, J.A.; McCloskey, C. Adverse Sedation Events in Pediatrics: Analysis of Medications Used for Sedation. *Pediatrics* **2000**, *106*, 633–644, doi:10.1542/peds.106.4.633.
138. Coté, C.J.; Notterman, D.A.; Karl, H.W.; Weinberg, J.A.; McCloskey, C. Adverse Sedation Events in Pediatrics: A Critical Incident Analysis of Contributing Factors. *Pediatrics* **2000**, *105*, 805–814, doi:10.1542/peds.105.4.805.
139. Gamble, C.; Gamble, J.; Seal, R.; Wright, R.B.; Ali, S. Bispectral Analysis during Procedural Sedation in the Pediatric Emergency Department. *Pediatr Emerg Care* **2012**, *28*, 1003–1008, doi:10.1097/PEC.0b013e31826ca956.
140. Malviya, S.; Voepel-Lewis, T.; Tait, A.R.; Merkel, S.; Tremper, K.; Naughton, N. Depth of Sedation in Children Undergoing Computed Tomography: Validity and Reliability of the University of Michigan Sedation Scale (UMSS). *Br J Anaesth* **2002**, *88*, 241–245, doi:10.1093/bja/88.2.241.
141. Dial, S.; Silver, P.; Bock, K.; Sagy, M. Pediatric Sedation for Procedures Titrated to a Desired Degree of Immobility Results in Unpredictable Depth of Sedation. *Pediatr Emerg Care* **2001**, *17*, 414–420, doi:10.1097/00006565-200112000-00004.
142. Full-Guideline-136287325.Pdf.
143. BCCH_ED_Sedation - Procedural Sedation and Analgesia Guideline 2013.Pdf.
144. Green, S.M.; Roback, M.G.; Miner, J.R.; Burton, J.H.; Krauss, B. Fasting and Emergency Department Procedural Sedation and Analgesia: A Consensus-Based Clinical Practice Advisory. *Ann Emerg Med* **2007**, *49*, 454–461, doi:10.1016/j.annemergmed.2006.08.017.
145. Sahyoun, C.; Cantais, A.; Gervaix, A.; Bressan, S.; Löllgen, R.; Krauss, B.; Pediatric Emergency Medicine Comfort and Analgesia Research in Europe (PemCARE) group of the Research in European Pediatric Emergency Medicine Pediatric Procedural Sedation and Analgesia in the Emergency Department: Surveying the Current European Practice. *Eur J Pediatr* **2021**, *180*, 1799–1813, doi:10.1007/s00431-021-03930-6.
146. Bevacqua, M.; Sforzi, I.; Bressan, S.; Barbi, E.; Sahyoun, C. Procedural Sedation and Analgesia in Italian Pediatric Emergency Departments: A Subgroup Analysis in Italian Hospitals. *Ital J Pediatr* **2023**, *49*, 23, doi:10.1186/s13052-023-01426-7.
147. Ramaiah, R.; Bhananker, S. Pediatric Procedural Sedation and Analgesia Outside the Operating Room: Anticipating, Avoiding and Managing Complications. *Expert Rev Neurother* **2011**, *11*, 755–763, doi:10.1586/ern.11.52.
148. Crego, N. Procedural Sedation Practice: A Review of Current Nursing Standards. *J Nurs Regul* **2015**, *6*, 50–56, doi:10.1016/S2155-8256(15)30010-7.
149. Green, S.M.; Norse, A.B.; Jackson, B.F.; Carman, M.J.; Roback, M.G.; ACEP Regulatory Challenges to Emergency Department Procedural Sedation Task Force Regulatory Challenges to Emergency Medicine Procedural Sedation. *Ann Emerg Med* **2021**, *77*, 91–102, doi:10.1016/j.annemergmed.2020.08.004.
150. Jo, Y.Y.; Kwak, H.J. Sedation Strategies for Procedures Outside the Operating Room. *Yonsei Med J* **2019**, *60*, 491–499, doi:10.3349/ymj.2019.60.6.491.
151. Rizzi, M.; Panzera, F.; Panzera, D.; D'Ascoli, B. Safety, Efficacy and High-Quality Standards of Gastrointestinal Endoscopy Procedures in Personalized Sedoanalgesia Managed by the Gastroenterologist: A Retrospective Study. *J Pers Med* **2022**, *12*, 1171, doi:10.3390/jpm12071171.
152. Blayney, M.R. Procedural Sedation for Adult Patients: An Overview. *Continuing Education in Anaesthesia Critical Care & Pain* **2012**, *12*, 176–180, doi:10.1093/bjaceaccp/mks016.
153. Mason, K.P.; Seth, N. Future of Paediatric Sedation: Towards a Unified Goal of Improving Practice. *Br J Anaesth* **2019**, *122*, 652–661, doi:10.1016/j.bja.2019.01.025.
154. Khamis AlBedwawi, A.; Bakheet Almansoori, A.; Abdelaziz Aljasmi, M.; Salem Al Ameri, F.; Ahmed, N.; Adnan Al Mnaseer, A.-S.; Mohamed Al Ramahi, I.; Charles Dittrich, K.; Qayyum, H. Procedural Sedation in a UAE Emergency Department: Encouraging Informed Decision-Making Through a Patient Information Leaflet. *Cureus* **2023**, *15*, e44980, doi:10.7759/cureus.44980.
155. Lee, A.; Shirley, M. Remimazolam: A Review in Procedural Sedation. *Drugs* **2021**, *81*, 1193–1201, doi:10.1007/s40265-021-01544-8.
156. Stöhr, T.; Colin, P.J.; Ossig, J.; Pesic, M.; Borkett, K.; Winkle, P.; Struys, M.M.R.F.; Schippers, F. Pharmacokinetic Properties of Remimazolam in Subjects with Hepatic or Renal Impairment. *Br J Anaesth* **2021**, *127*, 415–423, doi:10.1016/j.bja.2021.05.027.
157. Saunders, R.; Struys, M.M.R.F.; Pollock, R.F.; Mestek, M.; Lightdale, J.R. Patient Safety during Procedural Sedation Using Capnography Monitoring: A Systematic Review and Meta-Analysis. *BMJ Open* **2017**, *7*, e013402, doi:10.1136/bmjopen-2016-013402.
158. Baytaş, V.; Vural, Ç.; Özçelik, M.; Torres, R.T.; Saunders, R.; Alkış, N. Patient Safety during Propofol Sedation before and after Implementation of Capnography Monitoring. *J Clin Med* **2023**, *12*, 5959, doi:10.3390/jcm12185959.

 doi:10.20944/preprints202403.1360.v1

159. Shirane, S.; Funakoshi, H.; Takahashi, J.; Homma, Y.; Norii, T. Association between Capnography and Recovery Time after Procedural Sedation and Analgesia in the Emergency Department. *Acute Med Surg* **2023**, *10*, e901, doi:10.1002/ams2.901.
160. Toney, M.; Pattishall, S.; Garber, M. The Time Is Now: Standardized Sedation Training for Pediatric Hospitalists. *Pediatrics* **2020**, *145*, e20200446, doi:10.1542/peds.2020-0446.
161. Hooper, M.C.; Kamat, P.P.; Couloures, K.G. Evaluating the Need for Pediatric Procedural Sedation Training in Pediatric Critical Care Medicine Fellowship. *Pediatr Crit Care Med* **2019**, *20*, 259–261, doi:10.1097/PCC.0000000000001809.