LITHUANIAN UNIVERSITY OF HEALTH SCIENCES

MEDICAL ACADEMY

FACULTY OF MEDICINE

DEPARTMENT OF EMERGENCY MEDICINE

Drug Selection for Procedural Sedation in Emergency Medicine Department

Author/Student: Nadim Abou Assi

Supervisor: Vytautas Aukštakalnis , MD

Kaunas, 2022

Table of Contents

1. ABSTRACT

Drug Selection for Procedural Sedation in Emergency Medicine Department

Aim: To review the optimality of current drugs selected for procedural sedation in the Emergency Medicine Department.

Objectives: 1. To evaluate the most common drugs currently in use in the emergency medicine department for procedural sedation. 2. To determine the effects, benefits, and risks of each of those drugs. 3. To describe the effectiveness of these drugs about risks and benefits 4. To highlight the optimal drug selection and sedation level that would suit different procedures in the EMD.

Materials and methods: A search for articles was carried out using the PubMed electronic database with “Procedural Sedation” AND “Emergency Department” AND “Propofol” AND “Ketamine” AND “Ketofol” as keywords. Out of 882 studies found, 15 studies fit the inclusion criteria and the rest were excluded. The systematic reviews were reported with the PRISMA set.

Results: The review consisted of 13 randomized controlled clinical trials, 1 observational study and 1 convenience sample study. Sample sizes ranged from 61 to 904 study subjects. The studies about Ketamine showed it to have shorter recovery time and better hemodynamic stability than other drugs such as midazolam and haloperidol. Ketamine is also more tolerated in children due to lower ADRs. The study on propofol focused on the drug’s most common problem which is controlling the sedation level between moderate and deep sedation causing dose-related cardiorespiratory depression, the study found that mild sedation resulted in a lower rate of ADRs and that targeting mild sedation provides adequate amnesia with less need for supportive airway interventions than a target level of deep sedation. Additionally, the Ketofol studies showed that the use of Ketofol is more optimal than ketamine and propofol alone due to better recovery, shorter time, and less ADRs in both children and adults.

Conclusion: Propofol, and ketamine are typically first-line medications in the emergency department for procedural sedation, with the recent “ketofol” mixture being recently introduced as the combination of both. Propofol is effective in brief procedures in the emergency department, it is optimal in elderly patients, obese patients, pregnant women, and adults patients requiring fast sedation. However, it does not have analgesic effects and requires an analgesic agent to reduce the pain.

Ketamine is optimal in most procedures in the EMD and seems to be a superior choice to propofol due to its highly desired properties.

“Ketofol” seems to reduce overall adverse drug reactions of both drugs, it has shown to be optimal in adults and children, especially for its hemodynamic stability and emergence reaction. although it is not yet extensively studied and more research is recommended.

SANTRAUKA

Tikslas: Apžvelgti Skubios pagalbos skyriuje procedūriniai sedacijai naudojamus vaistus

Tikslai: 1. Įvertinti šiuo metu skubios medicinos pagalbos skyriuje dažniausiai naudojamus vaistus procedūriniai sedacijai. 2. Nustatyti kiekvieno vaisto efektyvumą, naudą ir riziką. 3. Apibūdinti šių vaistų veiksmingumą, atsižvelgiant į riziką ir naudą. 4. Išryškinti optimalų vaistų pasirinkimą ir sedacijos lygį, kuris tiktų įvairioms EMD procedūroms.

Medžiagos ir metodai: Straipsnių paieška atlikta naudojant PubMed elektroninę duomenų bazę su raktiniais žodžiais „Procedural Sedation“ ir „Emergency Department“ ir „Propofol“ ir „Ketamine“ ir „Ketofol“. Iš 882 nustatytų tyrimų 15 tyrimų atitiko įtraukimo kriterijus, o kiti buvo atmesti. Sisteminės apžvalgos buvo pateiktos naudojant PRISMA rinkinį.

Rezultatai: peržiūrą sudarė 13 atsitiktinių imčių kontroliuojamų klinikinių tyrimų, 1 stebėjimo tyrimas ir 1 patogumo imties tyrimas. Imčių dydis svyravo nuo 61 iki 904 tiriamųjų. Ketamino tyrimai parodė, trumpesnis kuno atsistatymo laikas ir hemodinamikos stabilumas yra geresnis nei kiti vaistai, tokie kaip midazolamas ir haloperidolis. Ketaminas taip pat gerai toleruojamas vaikų, kas lemia mažiau nepageidaujamų reakcijų. Propofolio tyrime kalbama apie dažniausiai pasitaikančią vaisto problemą – sedacijos lygio kontrolę. Tyrimas parodė, kad lengva sedacija užtikrina pakankamą amneziją ir mažiau reikia pagalbinių kvėpavimo takų intervencijų nei tikslinis gilios sedacijos. Be to, ketofolio tyrimai parodė, kad ketofolio vartojimas yra optimalesnis nei vien ketamino ir propofolio dėl trumpesnio kuno atsistatymo laiko ir mažesnio šalutinio poveikio vaikams ir suaugusiems.

Išvada: Propofolis, ketaminas yra įprasti pirmosios eilės vaistai skubios pagalbos skyriuje, skirti procedūriniai sedacijai, o „ketofolis“ neseniai buvo pristatytas kaip abiejų derinys.

Propofolis veiksmingas atliekant trumpas procedūras skubios pagalbos skyriuje, jis yra optimalus vyresnio amžiaus, nutukusiems, nėsčiosios ir suaugusiems pacientams, kuriems reikalinga greita sedacija. tačiau jis neturi analgezinio poveikio, tad skausmui sumažinti reikalingas analgetikas.

Ketaminas yra optimalus daugumoje skubios medicinos pagalbos procedūrų ir atrodo geresnis pasirinkimas nei propofolis dėl labai pageidaujamų savybių.

Atrodo, kad „ketofolis“ sumažina abiejų vaistų nepageidaujamas reakcijas. Įrodyta, kad jis yra optimalus suaugusiesiems ir vaikams, ypač dėl hemodinaminio stabilumo ir psichotropinės reakcijos. Tačiau ji dar nėra plačiai ištirta ir rekomenduojama atlikti daugiau tyrimų.

2. ACKNOWLEDGMENT

I want to extend my sincere gratitude to my supervisor, Prof. Dinas Vaitkaitis, and my consultant assistant. Vytautas Aukštakalnis for their kind and patient support.

3. CONFLICTS OF INTERESTS

There is no conflict of interest

4. ABBREVIATIONS

ED: Emergency Department

EMD: Emergency Medical Department

EP: Emergency Physician

PS: Procedural Sedation

PSA: Procedural Sedation and Analgesia

OR: Operating Room

ADE: Adverse Drug Events

ECG: Electrocardiogram

SpO2: Saturation of Peripheral Oxygen

EtCO2: End-tidal CO2

WHO: World Health Organization

PO: Per OS

IN: Intra Nasal

IM: Intramuscular

PRN: Pro re nata (according to need)

O_2: Oxygen

N_2O: Nitrous Oxide

SBP: Systolic Blood Pressure

DBP: Diastolic Blood Pressure

DCC: Direct Current Cardioversion

VAS: Visual Analog Scale

NGT: Nasogastric Tube

RASS: Richmond Agitation-Sedation Scale

MS: Mild Sedation

DS: Deep Sedation

ADR: Adverse Drug Reactions

5. INTRODUCTION

It is often said that pain is inevitable but suffering is optional. Procedural sedation refers to various techniques, medications, and techniques performed to help the patient tolerate displeasing or painful procedures and avoid traumatic experiences associated with such procedures. Since the proper use of procedural sedation also aims to decrease the patient's perception of pain it is generally achieved through the administration of analgesics combined with a sedative. Additionally, PS increases the chances of a successful procedure while decreasing the time required to perform it. As well as, it increases safety for the patient and personnel attending to the patient. These approaches include medications, psychological techniques, and/or physical maneuvers to achieve the intended effect [1]. Many painful and worrisome procedures do not require general anesthesia or the OR, these procedures can be safely, efficiently, and cost-effectively performed in a suitable environment such as the emergency room. Procedural sedation is commonly used in Europe and publications are on the rise, despite that, the collective European PSA experience has not been thoroughly described [2].
Since sedation is a continuum, it is not always possible to anticipate how each individual will respond physiologically to the sedative being administered which in turn could result in different threatening complications including but not limited to respiratory depression and upper airway obstruction.

Thus aiming for conscious sedation as a target state by carefully titrating and controlling the effects on the patient as an individual and the type of procedure is paramount to patient safety throughout the entirety of the procedure being performed. This is the rationale behind proper drug selection for procedural sedation in the ED.

Some guidelines and recommendations have been defined and determined for the administration of procedural sedatives and analgesics. However, further safety nets such as drug selection and the control of sedation levels for different procedures in the ED are currently present in insufficient quantities [2].

Therefore this systematic review aimed to determine the optimality of the current drugs selected and that are in use for procedural sedation during common painful procedures in the ED including abscess drainage wound exploration and suturing, and manipulation of fractures and dislocations in reducing pain and anxiety for patients undergoing these procedures.

6. AIM AND OBJECTIVES

Aim:

To determine the optimality of current drugs selected for procedural sedation in the Emergency Medicine Department.

Objectives:

1. To evaluate the most common drugs currently in use in the emergency medicine department for procedural sedation.
2. To determine the effects, benefits, and risks of each of those drugs.
3. To describe the effectiveness of these drugs' risks and benefits.
4. To highlight the optimal drug selection and sedation level that would suit different procedures in the emergency medical department.

7. LITERATURE REVIEW

Drug Selection for Procedural Sedation in the Emergency Medicine Department

7.1. Definition

According to the American College of Emergency Physicians (ACEP), Procedural sedation is a type of sedative administration with or without analgesics used to induce a state of sedation that enables the patient to tolerate painful and unpleasant procedures while maintaining cardiorespiratory function. PSA aims to achieve a depressed level of consciousness that allows the patient to maintain independent airway control and oxygenation [3].

7.2. Levels of Sedation

Sedation from mild, moderate, and deep levels of altered consciousness are often cited in the medical literature. It should be seen as decreased level of consciousness on a continuum of sedation that eventually leads to general anesthesia [4].

Minimal sedation is a drug-induced state in which the patient is at a baseline level of alertness, responding normally to verbal commands. Although cognitive function and coordination might be impaired cardiovascular and respiratory functions are unaffected. In the ED, minimal sedation is commonly administered to facilitate minor procedures [4,5].

Moderate sedation describes a drug-induced state of depressed consciousness during which the patient responds purposefully to verbal commands or tactile stimuli. No interventions are needed to maintain a patent airway and spontaneous ventilation is adequate. Cardiovascular function is maintained. Some patients during moderate sedation exhibit eyelid ptosis, slurred speech, and delayed responses to verbal stimuli. Event amnesia will often occur in moderate sedation levels. In the ED, moderate sedation is usually reached with the administration of benzodiazepine often in conjunction with an opioid such as fentanyl [4]. The term “conscious sedation,” which was often used in the past, roughly correlates with moderate sedation. The term is no longer recommended. The transition between having and then losing constant verbal contact with the patient occurs between moderate and deep sedation [6].

Dissociative sedation is a trance-like cataleptic state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability [7]. Ketamine is most commonly administered in the ED to evoke dissociative levels of sedation. This can facilitate moderate to severely painful procedures, as well as procedure that involve uncooperative patients [4].

Deep sedation: Deep sedation is a pharmacologically induced depression of consciousness during which the patient is not easily aroused but does respond purposefully after repeated painful stimulation. Maintaining ventilatory function may be impaired. The patient may need assistance in keeping a patent airway and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained [7]. Monitoring for a reduction in ventilation and cardiovascular complications should be done, including changes to pulse rate, heart rhythm, and blood pressure. Deep sedation is commonly achieved with short-acting sedative agents such as propofol, etomidate, or benzodiazepine. For painful procedures, an opioid such as fentanyl or morphine sulfate may be used with the sedative [4].

General anesthesia: General anesthesia is a depth of sedation characterized by unresponsiveness to all stimuli and the absence of airway protective reflexes, it is a drug-induced loss of consciousness during which patients are not responsive even to painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, also positive-pressure ventilation is necessary because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired [4,7]. Generally, it is accepted that, due to patients' variations in sensitivities to medications as well as comorbidities, patients may slip into a deeper level than anticipated; the operator must be well aware and prepared for this event [6].

7.3 Main Principles

Properly tolerated PSA results in preservation of airway patency and spontaneous ventilation despite levels of consciousness being depressed. However, even when adequately performed, PSA may increase the risk of morbidity and mortality in addition to the diagnostic/therapeutic procedure itself [8]. The safety of procedural sedation will be optimized only if practitioners use defined methods of sedation for which they have received formal training specialty-specific guidance [5].

7.3.1 Indications

Inadequate pre-assessment is a recurring factor in sedation related ADE and poor outcomes in all specialties [5] All patients receiving procedural sedation in the ED require a pre-assessment before sedation, including screening for any factors that might put a patient at a higher risk for PS. assessments may be brief or abbreviated during emergency cases [9].

Pre-sedation assessment must include the documentation of an accurate past medical and surgical history, identifying co-morbidities that might be a risk factor, patient medications and allergies, and the indications for the procedure. A focused physical examination and specific investigations must also be performed. The type of procedural sedation, risks and complications, and possible alternatives must be discussed with the patient and must be documented in the health record [6].

PSA is indicated any time a patient requires an intervention that will cause substantial discomfort. The level of sedation depends on the amount of pain the patient is most probably going to experience and the necessity to remain still during the length of the procedure. For example, an orthopedic procedure that requires joint manipulation and muscle relaxation will require deeper sedation than a procedure that is less troublesome. Decision-making must take into account the vital signs and how stable the patient is. A patient who cannot tolerate hypoventilation or hypotension may be better suited for a dissociative agent rather than moderate to deep sedation [1]. The system that is most often used for clinical assessment is the ASA Physical Status (Class) scoring

1. ASA Class 1: Normal healthy patient with no organic, physiologic, or psychiatric disturbance.
2. ASA Class 2: Patients presenting with mild systemic disease.
3. ASA Class 3. Patients with severe systemic disease.
4. ASA Class 4. Patients with severe systemic disease represent a constant threat to life.
5. ASA Class 5. Moribund patients are not expected to survive without the operation.
6. ASA Class 6. A patient that is declared clinically dead and whose organs are being donated.
7. The addition of “E” to physical status denotes an emergency procedure. The definition of an emergency is as exists when a delay in treatment of the patient would lead to a significant increase in the threat to life or body part [1,10-15].

Based on those indications and risk factors, it is recommended that EPs evaluate the target sedation levels, the need for drug combinations, and choose medications based on the probability of ADEs [16,17].

Table 1 summarizes the major indications of PSA in North America, Europe & Japan.

(Yosuke Homma, Tatsuya Norii, Takeshi Kanazawa, et al.) [17]

Frequency Rating	Country: Netherlands	Country: United States	Country Japan
1	Fracture or Dislocation	Fracture or Dislocation	Cardioversion
2	Abscess Drainage	Lumbar Puncture	EGD
3	Cardioversion	CT	Fracture or Dislocation
4	Tube Thoracostomy	Foreign Body Removal	Laceration Repair
5	Lumbar Puncture	Tube Thoracostomy	MRI

CT, computed tomography; EGD, esophagogastroduodenoscopy; MRI, magnetic resonance imaging; PSA, procedural sedation, and analgesia. The frequency rate in this table is the ranking order of the most commonly seen cases that require PSA in the mentioned countries.

7.3.2 Contraindications

In some situations, PSA is contraindicated.

- EP training. If the person performing the sedation lacks the skill set to secure an unstable airway, from intubation to cricothyrotomy, PSA is not an option [1].
- Monitoring and resuscitation equipment are not available [1].
- Patient needs. If the patient requires more than a brief painful procedure (e.g., surgery,) general anesthesia in the OR is more suitable [1].
- Patient's condition. PSA is contraindicated in patients with an ASA classification of unstable class II or class IV and above (unless immediate intervention is imperative) [1].

7.3.3 Equipment

Before starting a PS and depending on the level of sedation, the EP should have available and at hand the equipment for operational readiness which will ensure the safety and success of the PS [1].

• IV fluids, lines, and saline lock

• Medications and equipment for cardiac resuscitation

• Oxygen administration equipment

• Suctioning device

• Airway equipment including bag valve mask, laryngeal mask airway, bougie, direct or video-assisted laryngoscopy with appropriate blades, appropriately sized oral airways, and endotracheal tubes, surgical and needle airways

• Reversal drugs when using drug-reversible agents such as opioids and benzodiazepines. Naloxone and flumazenil effectively stop the effects of fentanyl (or of other opioids) and midazolam (or of other benzodiazepines), respectively. personnel should be aware that flumazenil use can be associated with status epilepticus in patients with unidentified benzodiazepine abuse or if the patient has a seizure disorder.

• Monitoring equipment: ECG, blood pressure monitor, SpO2 monitor, EtCO2 monitor is highly desirable

7.3.4 Personnel

Ideally, there must be a two EP sedation team. One performs the intended procedure, whereas the second EP will be dedicated to sedation, patient monitoring, and team coordination. Unfortunately, there are many circumstances where having two operators is not possible, particularly in emergency and unplanned procedures. Personnel involved in PSA must have the following training [1]:

• Perform proper patient selection

• Perform advanced airway-management skills (this is a mandatory skill)

• Understand and manage each of the medications being administered

• Perform careful patient monitoring

• Manages all potential complications that might arise from PS

7.3.5 Preparation

It must be ensured that procedural sedation takes place in the resuscitation room or another room that contains advanced life support equipment. The sedation team must record the patient's vital signs such as pulse and respiratory rate, BP, ECG, SpO2 before, during, and after the procedure. EtCO2 monitoring and supplementary oxygen is recommended for patients in which deeper levels of sedation are intended. The team should ideally, before starting the procedure, check the patient, the monitoring devices, the equipment, the needed medications are available, personnel, etc... [19].

7.4 Drug Selection

In the Emergency Departments, EPs perform brief procedures and most patients require a brief PSA, especially since some of these patients are never admitted to the hospital. Therefore, it is important to administer sedatives and analgesics in small, incrementally progressive doses while

keeping surveillance on the patient's reaction to avoid an excessive dose administration. Any additional dose must be given after peak time, to allow time for the drug concentrations in the brain to reach their maximum. Because these agents do not have both hypnotic and analgesic effects, it is sometimes needed to use them in combination. For example, the combination of ketamine and propofol (ketofol) has been showing some success and grabbing interest [17,20-23].

Table 2 summarizes these characteristics, peak time, and effectiveness for three major PSA drugs Propofol, Ketamine, and Ketofol [17,20-27].

Drug	**Route**	**Dosing*, Initial Dose (Additional Dose)**	**Onset, min**	**Peak, min**	**Duration**, min**	**Contraindications**
Propofol	IV	Adult: 0.5-1.5 mg/kg (0.2-0.5 mg/kg by 0.5-1 min) Elderly: 0.5 mg/kg or less ≤3 year old: 2.0 mg/kg Pediatric: 1.5 mg/kg	0.5-1	1–1.5	5-10	

Ketamine	IV, IM	IV: 1–1.5 mg/kg (0.5–1 mg/kg by 2 min) IM: 4–5 mg/kg (2–5 mg/kg)	IV: 0.5–1 IM: 5	IV: 1 IM: 5	IV: 10–15 IM: 20-30	Infants <3 months of age Schizophrenia
Ketofol (combination of Ketamine + Propofol)	IV	0.5 mg/kg for each ketamine and propofol (0.1–0.25 mg/kg, respectively)	0.5–1	1	10–15	Infants <3 months of age Schizophrenia

* Ideal body weight.

** In a single dose.

Propofol:

Advantages: ultra-fast sedative and amnestic, takes effect within 40 seconds upon administration. It is also highly lipophilic thus crosses the blood-brain barrier swiftly [28].

Disadvantages: Propofol has no analgesic effect hence it is often recommended to combine it with an additional opioid (fentanyl, typically 50-100mcg) or ketamine [28].

Common side effects include hypotension due to cardiovascular depression, which often leads to complications in patients with severe conditions such as sepsis, cardiac dysfunction or hypovolemia [29,30].

Additionally, respiratory depression manifesting as mild desaturation is also seen in PSA when using propofol, it is exacerbated by the co-administration of other sedatives or analgesics. However, these episodes often require short periods of supplemental oxygen and even less often assisted ventilation with a bag-valve mask. There have been no reports of endotracheal intubation due to propofol-induced respiratory depression during procedural sedation. [29,30].

Ketamine:

Advantages: Ketamine provides sedation, analgesia, and amnesia, preserving upper airway tone and maintaining protective airway reflexes as well as spontaneous breathing. It has a rapid onset, short duration with optimal analgo-sedative properties, often used for short and painful procedures, such as reductions or laceration repair [28].

Disadvantages: The common side effects of ketamine include but not limited to; tachycardia and hypertension which are usually mild and transient.

Laryngospasm, is usually seen in patients with anatomical abnormalities for example tracheal stenosis, also in patients undergoing procedures that involve prolonged stimulation of the oro-pharynx. These can be minimized by using suction devices to prevent accumulation of secretions in the posterior part of the oropharynx [28].

Emergence reactions are the most commonly reported side effect, they may vary in intensity but often manifest as disorientation, hallucinations and experiences which are described as terror and nightmares. They occur in about 20% of adults but can be prevented by premedication with midazolam 0.05 mg/kg by IV [28]. Ketamine can exacerbate schizophrenia and should be avoided in patients with this condition.

"**Ketofol" (Combined Ketamine and Propofol)**

Advantage: The idea of "ketofol" is that the benefits of the two medications work synergistically and a lower dose of each drug is needed, thus reducing the risk for potential side effects of propofol-induced hypotension and ketamine-induced vomiting or emergence reactions [28,31].

Disadvantage: Not enough studies that clearly show the clinical significance of improved outcomes or reduced complications during PSA [28].

7.5 Special Considerations:

In some special cases such as pregnancy, elderly, obese patients and higher risk patients, PSA must be carefully considered following a case-by-case approach, with the relative risks and benefits that may arise from procedural sedation [28]. The most common special considerations are the following:

Patients at risk of hypotension:

Patients with the risk of hypotension from recent illness or dehydration, cardiac disease, or any other condition that puts them at risk of hypotension. Ketamine is best suited as PSA in comparison to propofol due to the fact that propofol reduces blood pressure far greater than ketamine [28].

Patient at risk for airway complications:

Patients who have a compromised airway or respiratory function are better off with Ketamine as PSA since it ensures the maintenance of protective airway reflexes and does not lead to respiratory depression [28].

Elderly patients

Elderly patients often are at increased risk of complications during PSA regardless of the drug selected. Hence procedural sedation should always start at a lower dose, with slower rates of infusion and less frequent administration [28].

For elderly patients without severe comorbidities, the optimal drug selection is propofol due to it being an ultrashort-acting sedative. Moreover, patients with major comorbidities are preferably handled in the operating room.

Obese patients

In obese patients, adjusting drug doses are usually necessary when providing PSA because of physiologic changes and related health problems (sleep apnea and restrictive lung disease). These patients are often predisposed to hypoxemia and ventilation difficulties [32].

Procedural sedation in obese patients is associated with more habitual need for airway intervention such as bag-mask ventilation and more frequent although it does not increase the incidence of serious ADEs [28]. However, obesity does affect the choice drug selection and dosing, generally, doses should be based on lean body weight in order to avoid over-sedation.

In the case of propofol, the initial dose is based on the patient's ideal body weight then supplemental doses are titrated as required in order to achieve the desired level of sedation. Propofol is highly dependent on cardiac output, which is often elevated in obese individuals. Propofol is also very lipophilic thus having a greater volume of distribution in these patients. All the aforementioned factors lead to an increased clearance rate and a shorter duration of effect [28].

In the case of ketamine, the patient’s ideal body weight is also used to determine the initial dosing for sedation then doses provided are added as needed [28].

Pregnant patients

In the case of pregnancy, pre-procedural preparation is crucial, medication that reduces gastric volume and increases gastric sphincter tone such as metoclopramide must be administered as well as, a drug that decreases stomach acidity for example H2 antagonists or sodium citrate, will help reduce the risk of emesis and aspiration. Moreover, maintaining good hydration and left lateral displacement of the uterus (at the end of second trimester and the third trimester) reduces the risk of utero-placental insufficiency, hypotension and thus decreases the risk of fetal hypoxemia. During PSA, the addition of oxygen via face-mask is administered to decrease the maternal desaturation caused by sedation (due to

decreased functional residual capacity) [28]. Propofol commonly causes hypotension in pregnant women, however it does maintain appropriate umbilical blood flow due to the dilating effect it has on umbilical circulation.

So far, there has been no human or animal studies that show evidence of the teratogenicity of propofol, although there are some concerns about neonatal depression especially when used in high doses and close to the delivery date [33].

Additionally, ketamine has shown to be a cause of maternal hypertension and increases heart rate up to 40%, and therefore is not recommended for use in pregnant women with known hypertensive disease.

Neonatal depression is a also a concern, when ketamine is given close to delivery.

In summary, due to limited data that is available on ketamine as PSA during pregnancy, it may be used in low doses throughout pregnancy, but other agents may be preferable and far more optimal [33].

7.6 Complications

Complications related to PSA and AEs are common, most importantly respiratory events. For instance, geriatric patients, the sedation with multiple drug within 60 minutes, and patients that have alcohol intoxication increase the risk of developing such complications [34].

Most fatal incidents are due to inadequate oxygenation or poor ventilation in a non-operating setting of inadequately equipped monitoring facilities as well as the inability to prevent and manage over-sedation [35].

Estimated incidence per 1,000 patients with 95% CI for agitation, apnea, aspiration, bradycardia, bradypnea, hypotension, hypoxia, intubation, laryngospasm, nausea, and vomiting [36].

Most Frequent Adverse Events:[36]

- Hypoxia: 40.2 per 1,000 sedations.
- Vomiting: 16.4 per 1,000 sedations.
- Hypotension: 15.2 per 1,000 sedations.
- Apnea: 12.4 per 1,000 sedations.

Severe Adverse Events Requiring Emergent Medical Intervention:[36]

- Aspiration 1.2 per 1,000 sedations.
- Laryngospasm: 4.2 per 1,000 sedations.
- Intubation: 1.6 per 1,000 sedations.

7.7 Management:

The main focus should be on maintaining good oxygenation and the prevention of respiratory suppression, which is done by monitoring, especially EtCO2 (by capnography), also having a low threshold to support respiration with bag valve mask ventilation, the respiratory support of the patient should be regarded as a necessary intervention rather than an adverse outcome. Since hypotension is also a complication, it is essential to have an IV in place and be prepared to support blood pressure with IV fluids [1], as well as ECG and SpO2 monitoring during sedation. Furthermore, The patient must be moved carefully from recumbent to sitting position and have the proper training in managing other potential complications such as vomiting to prevent choking by aspiration [1]. All personnel in charge of the PSA must be CPR certified. As a minimum, at least two people in the room should have CPR competency, they could both be intermediate life support trained, although advanced life support training would be preferable [37].

Monitoring the patient in recovery should be the same standard as during PSA. Patients must be monitored for at least 30 min during recovery and fulfill the recovery criteria before leveling down the degree of care. As recommended in the guidelines, the Aldrete score should be used for discharging the patient's home.[37], The Aldrete score is a scoring system that assesses activity, respiration, circulation, and color. A score of 8 to 10 is considered adequate for discharging the patient home [38].

8. METHODOLOGY

Systematic review search strategy for studies selection:

For this review, to include relevant articles for the literature search, a systematic search for suitable articles was carried out using the PubMed electronic database. Keywords for the search were: "Procedural Sedation" AND "Emergency Department" AND "Propofol" AND "Ketamine" AND "Ketofol", the last literature search was reviewed on the 15th of March 2022. A total of 882 studies were yielded and were subjected to further screening by applying the exclusion and inclusion criteria. Inclusion criteria are the full text of clinical trials and randomized controlled trials, within the last 10 years, conducted on humans and published in the English language, therefore, 845 articles were excluded and the 37 remaining articles were assessed manually for eligibility. 22 were found to be irrelevant based on title and abstract, Finally, 15 studies were reviewed and analyzed.

Table 3. Inclusion and Exclusion Criteria for the Study Selection

Inclusion Criteria	**Exclusion Criteria**
Publication date from 2012 to 2022	Published before 2012
English Language	Language other than English
Human Subjects	Animals
Clinical Trials, Randomized Controlled trials	Book, documents, Meta-Analysis, Review, Systematic Review
Full Text	Not Full text available
"Procedural Sedation" AND "Emergency Department" AND "Propofol" AND "Ketamine" AND "Ketofol"	

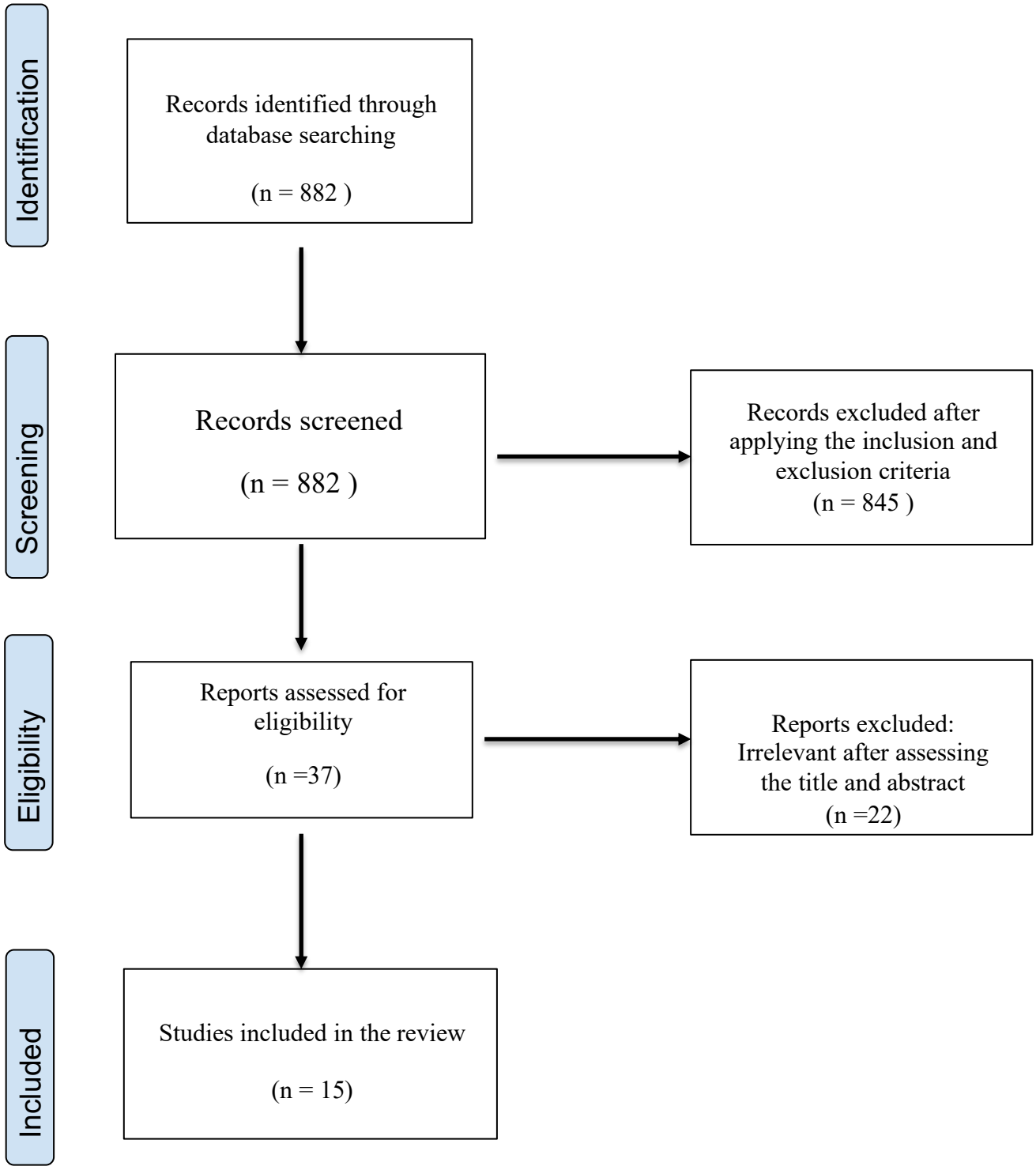

Figure 1. PRISMA (preferred reporting items for systematic reviews and Meta-Analysis) flow chart on the selection of articles included for further assessment in the results.

n- number of articles

9. RESULTS

The results of the literature review are summarized in the following Table 4.

Table 4. A list of selected articles was submitted for literature review.

Study Title. Publication Date. Author.	Study Type	Study Period and Sample Size (n)	Drug Selected	Outcome	Limitation of the study
Rapid Agitation Control With Ketamine in the Emergency Department: A Blinded, Randomized Controlled Trial. (2021) Barbic D. et al. [39]	Randomized Clinical Trial	June 2018, to March 2020 n=308	Ketamine	median time to sedation was 14.7 minutes for midazolam and haloperidol versus 5.8 minutes for ketamine In ED patients with severe agitation, intramuscular ketamine provided significantly shorter time to adequate sedation than a combination of intramuscular midazolam and haloperidol.	COVID-19-mandated restrictions

Randomized Clinical Trial Comparing Procedural Amnesia and Respiratory Depression Between Moderate and Deep Sedation With Propofol in the Emergency Department. (2019) Schick A. et al. [40]	Randomized Clinical Trial	March 2015, to May 2017. n=107	Propofol	Targeting Mild Sedation or Deep Sedation did not reliably result in the intended sedation level. Mild Sedation resulted in a lower rate of total AREs Mild Sedation provides adequate amnesia with less need for supportive airway interventions than a target level of Deep sedation.	none
Risk Factors for Sedation-related Events During Acute Agitation Management in the Emergency Department. (2019) Yap CYL. et al. [41]	Randomized clinical trial	2014 to 2017 n=904	Ketamine Propofol	patients presenting with acute agitation, especially those aged 65 years and older, intoxicated with alcohol, or managed with multiple types of parenteral sedation, carry increased risk of sedation-related adverse events.	none

Determination of the median effective dose of propofol in combination with different doses of ketamine during gastro-duodenoscopy in children: a randomized controlled trial (2018) Hayes J. et al [42]	Randomized clinical trial	December 2013 to May 2018 n=56	Ketamine Propofol	Ketamine at 0.5-1 mg/kg reduces the needed dose of propofol in general anaesthesia for gastro-duodenoscopy in children while also reducing the incidence of propofol related adverse haemodynamic effects.	only children
Adverse Events With Ketamine Versus Ketofol for Procedural Sedation on Adults: A Double-blind, Randomized Controlled Trial. (2017) Lemoel F. et al. [43]	Randomized Double blinded Clinical Trial	2017 n=152	Ketamine Ketofol	significant reduction in recovery reactions and emesis frequencies among adult patients receiving emergency procedural sedations with ketofol, compared with ketamine.	none

Ketamine as an Adjunct to Opioids for Acute Pain in the Emergency Department: A Randomized Controlled Trial. (2017) Bowers KJ. et al. [44]	randomized, double-blinded, placebo-controlled trial	2013 to 2015 n= 63	Ketamine	Patients treated with low-dose ketamine in addition to their opioid analgesia reported greater reduction in pain over time and similar satisfaction with their treatment to those treated with placebo in addition to their opioid analgesia.	none
Efficacy of oral ketamine compared to midazolam for sedation of children undergoing laceration repair: A double-blind, randomized, controlled trial. (2016) Rubinstein O. et al. [45]	double-blind randomized trial	January 2014 to June 2014 n= 68	Ketamine Midazolam	No difference in the level of pain was found between ketamine and midazolam treated patients. Compared with oral midazolam (0.7 mg/kg), oral ketamine (5 mg/kg) was associated with higher rates of sedation failure, and thus is not recommended as a single agent for oral sedation in children requiring laceration repair.	only pediatric

Randomized Controlled Feasibility Trial of Intranasal Ketamine Compared to Intranasal Fentanyl for Analgesia in Children with Suspected Extremity Fractures. (2017) Reynolds SL. et al. [46]	Randomized Clinical Trial	December 2015 to November 2016 n=629	Ketamine Fentanyl	Intranasal ketamine was associated with more minor side effects than intranasal fentanyl. Pain relief at 20 minutes was similar between groups	Only Pediatrics
Ketamine/propofol admixture (ketofol) at induction in the critically ill against etomidate (KEEP PACE trial): study protocol for a randomized controlled trial (2019) Smischney N. et al. [47]	Randomized Clinical Trial	2015 to 2019 n=160	Ketofol	In a critically ill population, ketamine/propofol admixture was not superior to a reduced dose of etomidate at preserving per-intubation hemodynamics and appears to be a safe alternative induction agent in the critically ill.	Non-blinded

Adjunctive Atropine Versus Metoclopramide: Can We Reduce Ketamine-associated Vomiting in Young Children? A Prospective, Randomized, Open, Controlled Study (2012) Lee JS. et al. [48]	Randomized Clinical Trial	October 2010 to September 2011. n= 338	Ketamine	Inability to reduce Ketamine associated vomiting using adjunctive atropine or metoclopramide and Ketamine associated vomiting often occurred after ED discharge.	only young children
The PICHFORK (Pain in Children Fentanyl or Ketamine) trial: a randomized controlled trial comparing intranasal ketamine and fentanyl for the relief of moderate to severe pain in children with limb injuries (2015) Graudins A. et al. [49]	Randomized clinical trial	2013 to 2014 n= 73	Ketamine	Intranasal fentanyl and ketamine were associated with similar pain reduction in children with moderate to severe pain from limb injury. However, Ketamine was associated with more minor adverse events.	only children

Ketamine-Propofol Combination (Ketofol) Versus Propofol Alone for Emergency Department Procedural Sedation and Analgesia: A Randomized Double-Blind Trial (2012) Andolfatto G. et al. [50]	Randomized clinical trial	December 2010-September 2011 n=284	Ketofol Propofol	Ketofol for ED procedural sedation does not result in a reduced incidence of adverse respiratory events compared with propofol alone. Induction time, efficacy, and sedation time were similar; however, sedation depth appeared to be more consistent with ketofol.	none
Comparison of ketamine/propofol (ketofol) and etomidate/fentanyl (etofen) combinations for procedural sedation and analgesia in the emergency department: An observational study (2017) Sanri E. et al. [51]	Observational Study	2017 n= 112	Ketofol	Etofen is a promising combination for the PSA of adult patients with lower respiratory AE and intervention rates and with better hemodynamic profile in comparison to Ketofol	only adults

Implementation of a protocol using ketamine-propofol ('ketofol') in a 1 to 4 ratio for procedural sedation in adults at a university hospital emergency department - report on safety and effectiveness (2021) Walravens S. et al. [52]	Convenience Sample Study	2021 n= 61	Ketofol	ketofol in a 1 to 4 ratio appears safe and effective for use in the emergency department.	non-consecutive and limited sample used
Comparison of effects of propofol and ketofol (Ketamine-Propofol mixture) on emergence agitation in children undergoing tonsillectomy (2019) Jalili S. et al. [53]	Randomized clinical trial	November 2017 to March 2018 n=87	Ketofol Propofol	Infusion of ketofol in children undergoing tonsillectomy provides shorter recovery time and lower incidence of EA despite the non-significant difference with propofol.	only children

10. DISCUSSION OF THE RESULTS

After a thorough evaluation of the studies reported, various drug selection options were found available, However, this literature review focuses on the three following drugs; Ketamine, Propofol and the combination of those two drugs known as “Ketofol”. The most influential factors on the outcomes and the patient prognosis are the adverse drug reactions, sedation levels, and type of drug selected during procedural sedation in the ED.

A study conducted by Celene Y.L, et al. evaluated the risk factors for sedation-related events during acute agitation management in the Emergency Department in Australia on 904 patients who experienced the following ADRs; oxygen desaturation (7.4%), airway obstruction (3.6%), bradycardia (1.9%), hypotension (1.7%), and prolonged QTc interval (1.3%). No deaths or serious ADRs were reported and found that sedation-related ADRs are common, especially respiratory events. Elderly patients, sedation with multiple sedatives within 60 minutes, and alcohol intoxication increased those risks [41].

Ketamine:

Ketamine is an NMDA- receptor antagonist, used to initiate and maintain anesthesia. It is well known for its pain-relieving, sedative, and amnesic effects. A distinct feature of Ketamine is the preservation of breathing and airway reflexes, it also increases blood pressure and acts as a bronchodilator. Barbic D. et al. found that patients with severe agitation in the ED had a significantly shorter time to adequate sedation using intramuscular ketamine than those who were given the intramuscular midazolam and haloperidol combination [39]. Bowers KJ. et al. also concluded in their study that patients treated with low-dose ketamine and opioid analgesia reported greater reduction in pain over 120 minutes and similar satisfaction with their treatment in comparison to those who were treated with placebo in addition to opioid analgesia (51% vs. 19%) respectively, while resulting in a lower total opioid dose as well as fewer repeat doses of analgesia [44]. Moreover, Hayes J. et al highlighted that Ketamine at 0.5-1 mg/kg reduces the needed dose of propofol in general anesthesia for gastro-duodenoscopy in children while also reducing the incidence of propofol related adverse hemodynamic effects [42]. In addition, a study conducted by Reynolds SL. et al. showed that intranasal ketamine was associated with more minor side effects than intranasal fentanyl and that at 20 minutes the pain relief was similar between groups [46]. A similar study by Graudins A. et al. found that intranasal fentanyl and ketamine were associated with similar pain reduction in children with moderate to severe pain from limb injury although Ketamine was associated with more minor adverse events [49].

However, for the side effect of vomiting from ketamine, a study by Lee JS. et al. reported the inability to reduce Ketamine associated vomiting using adjunctive atropine or metoclopramide and Ketamine associated vomiting often occurred after ED discharge [48]. Another study by Rubinstein O. et al. did not recommend oral Ketamine as a single agent for sedation in children undergoing laceration repair [45].

Propofol:

Propofol is a non-barbiturate sedative developed in Europe during the1970s and was eventually used by anesthesiologists. Propofol is prepared in a lipid emulsion, giving it the characteristic milky white appearance and the colloquial name "milk of amnesia". It may be administered as a bolus or an infusion, or some combination of the two[54-56]

Recently its use has spread into the ED as a part of procedural sedation. Its popularity as a PSA agent is growing because it has a desirable pharmacokinetic profile by conferring a quick onset and short recovery time [57]. Additionally it has the convenience of functioning as an antiemetic, anticonvulsant, and an amnestic agent [58]. However, the use of propofol is limited by a relatively high incidence of dose related cardio respiratory depression, thus one of the main concerns with propofol is controlling the sedation level between moderate and deep sedation [54-56,59].

A randomized clinical trial led by Schick A, et al. In the United States compared procedural amnesia and respiratory depression during moderate and deep sedation levels with propofol in the EMD. Doses, vital signs and observer's assessment of alertness/sedation (OAAS) score, end-tidal CO2 were monitored continuously. An image was shown intermittently each 30 seconds starting 3 minutes before the procedure and continued till the patient returned to baseline after the procedure. Recalling and recognizing the images were examined after 10 minutes from sedation. Subclinical respiratory depression was set as a level of $SpO2 \leq 91\%$, change in $ETCO2 \geq 10$ mmHg, or absent ETCO2 at any time. The study found that mild sedation resulted in a lower rate of total ADRs and fewer patients had multiple AREs with no difference in the procedural recall, the study recommended that targeting mild sedation provides adequate amnesia with less need for supportive airway interventions than a target level of deep sedation [40].

Ketofol:

"Ketofol" is a mixture of ketamine and propofol which results in a combination that appears to counteract each other's adverse effects, giving several advantages including hemodynamic stability. Ketofol is recently being used in bolus form to provide sedation and analgesia for painful procedures in the emergency room [28]. A study by Lemoel F. et al, found that significantly fewer patients

experienced emesis with ketofol compared with ketamine and reduction in recovery reactions [43]. Ketofol was shown to be more consistent in the depth of sedation compared to propofol alone for procedural sedation in the ED as it was concluded by the study of Andolfatto G. et al [50]. Additionally, in children, Jalili S. et al. found that an infusion of ketofol undergoing tonsillectomy provides shorter recovery time and lower incidence of emergence agitation (which is a state characterized by confusion, irritability, inconsolable crying, disorientation and non-cooperation often caused by anxiety, agitation on induction, rapid awakening in an unfamiliar environment, pain, airway distress and separation from parents) [53].

Moreover, In a heterogenous critically ill population, a study conducted by Smischney N. et al. concluded that ketofol appears to be a safe alternative induction agent to a reduced dose of etomidate at preserving pre-intubation hemodynamics [47].

Ketofol is often given in a 1:1 ratio of Ketamine and propofol respectively, Nonetheless, a study by Walravens S. et al. in 2021 reported that a 1:4 ratio of Ketofol appears to be safe and effective for use in the emergency department [52].

Although Ketofol seems to be a superior to most medications used for PSA in the ED, in 2017, Sanri E. et al. found that a combination of Etomidate and Fentanyl called “Etofen” is a promising combination for the PSA of adult patients with lower respiratory AE and intervention rates and with better hemodynamic profile in comparison to Ketofol [51]. However that study was only conducted on adult patients and may apply differently to a pediatric patient population.

11. CONCLUSIONS

1- Propofol and ketamine are typically first-line medications in the emergency department for procedural sedation, with the recent “ketofol” mixture being recently introduced as the combination of both. These procedural sedation drugs are often supplemented by ancillary drugs to improve some of their disadvantages such as midazolam, fentanyl etc…

2- Propofol is an extremely fast sedative and amnestic, however it does not have analgesic effects and has the risk of cardiopulmonary depression, moreover, the level of sedation needs to be closely monitored while using propofol as PSA. Ketamine successfully provides sedation, analgesia, and amnesia with rapid and short onset while also preserving protective respiratory reflexes and spontaneous breathing nevertheless it is commonly associated with emergence reactions and vomiting. “Ketofol” is a promising new combination of both Ketamine and propofol, which seems to reduce overall ADRs of both drugs while enhancing recovery time. although it is not yet extensively studied and more research is recommended.

3- Propofol is effective in brief procedures in the EMD such as cardio-version or lumbar puncture still however requiring an analgesic agent to reduce the pain during the procedure.
Ketamine is effective in most procedures in the EMD and seems to be a superior choice to propofol due to its highly desired properties.
Ketofol’s effectiveness remains under study nevertheless it is showing to be a promising combination.

4- Propofol is optimal in elderly patients, pregnant women, obese patients and adults also in patients requiring fast sedation. Ketamine is optimal in children, patients with high risk of hypotension or airway complications. Ketofol has shown to be optimal in adults and children especially for its hemodynamic stability and emergence reaction.

12. PRACTICAL RECOMMENDATIONS

Patient's individual status must be regarded while selecting a drug for PSA since every patient reacts differently to each drug. Drug selection in procedural sedation is not a "one size fits all" process. Sedation level is just as important as drug selection during procedural sedation and thus should always be kept in mind.

13. LITERATURE LIST

1. Benzoni T, Cascella M. Procedural Sedation. [Updated 2022 Jan 9]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK551685/

2. Cyril Sahyoun, Aymeric Cantais, Alain GervaixGervais, et al. Pediatric procedural sedation and analgesia in the emergency medical department: surveying the current European practice. European Journal of Pediatrics; 2021; 180: 1799-1813.

3. Green SM, Roback MG, Krauss BS, Miner JR, Schneider S, Kivela PD, Nelson LS, Chumpitazi CE, Fisher JD, Gesek D, Jackson B, Kamat P, Kowalenko T, Lewis B, Papo M, Phillips D, Ruff S, Runde D, Tobin T, Vafaie N, Vargo J, Walser E, Yealy DM, O'Connor RE. Unscheduled Procedural Sedation: A Multidisciplinary Consensus Practice Guideline. Ann Emerg Med. 2019 May;73(5):e51-e65

4. Godwin SA, Burton JH, Gerardo CJ, Hatten BW, Mace SE, Silvers SM, Fesmire FM. Clinical policy: procedural sedation and analgesia in the emergency department. Annals of emergency medicine. 2014 Feb 1;63(2):247-58.

5. Michael Roger Blayney, LDS RCS(Eng), BDS(Lond), MBChB(Birm), DA(UK), DRCOG, FRCA, Procedural sedation for adult patients: an overview, *Continuing Education in Anaesthesia Critical Care & Pain*, Volume 12, Issue 4, August 2012, Pages 176–180.

6. Dobson, G., Chong, M.A., Chow, L. *et al.* Procedural sedation: a position paper of the Canadian Anesthesiologists'Society, 2018. *Can J Anesth/J Can Anesth* 65, 1372–1384

7. American Society of Anesthesiologists. *Position on Monitored Anesthesia Care.*October 17, 2018. Available from:https://www.asahq.org/standards-and-guidelines/continuum-of-depth-of-sedation-definition-of-general-anesthesia-and-levels-of-sedationanalgesia

8. Hinkelbein, Jochen; Lamperti, Massimo; Akeson, Jonas; Santos, Joao; Costa, Joao; De Robertis, Edoardo; Longrois, Dan; Novak-Jankovic, Vesna; Petrini, Flavia; Struys, Michel M.R.F.; Veyckemans, Francis; Fuchs-Buder, Thomas*; Fitzgerald, Robert† European Society of

Anaesthesiology and European Board of Anaesthesiology guidelines for procedural sedation and analgesia in adults, European Journal of Anaesthesiology: January 2018 - Volume 35 - Issue 1 - p 6-24

9. Miller KA, Andolfatto G, Miner JR, Burton JH, Krauss BS. Clinical practice guideline for emergency department procedural sedation with propofol: 2018 update. Annals of emergency medicine. 2019 May 1;73(5):470-80.

10. Abouleish AE, Leib ML, Cohen NH. ASA provides examples to each ASA physical status class. *ASA Monitor* 2015; 79:38-9 http://monitor.pubs.asahq.org/article.aspx?articleid=2434536

11. Hurwitz EE, Simon M, Vinta SR, et al. Adding examples to the ASA-Physical Status classification improves correct assignments to patients. *Anesthesiology* 2017; 126:614-22

12. Mayhew D, Mendonca V, Murthy BVS. A review of ASA physical status – historical perspectives and modern developments. Anaesthesia 2019; 74:373-9

13. Leahy I, Berry JG, Johnson C, Crofton C, Staffa S, Ferrari LR. Does the Current ASA Physical Status Classification Represent the Chronic Disease Burden in Children Undergoing General Anesthesia? Anesthesia & Analgesia, October 2019;129(4):1175- 1180

14. Ferrari L, Leahy I, Staffa S, Johnson C, Crofton C, Methot C, Berry J. One Size Does Not Fit All: A Perspective on the American Society of Anesthesiologists Physical Status Classification for Pediatric Patients. Anesthesia & Analgesia, June 2020;130(6):1685-1692

15. Ferrari LR, Leahy I, Staffa SJ, Berry JG. The Pediatric Specific American Society of Anesthesiologists Physical Status Score: A Multi-center Study. Anesthesia & Analgesia 2020 (in press)

16. Green SM, Roback MG, Krauss BS *et al* Unscheduled procedural sedation: a multidisciplinary consensus practice guideline. *Ann. Emerg. Med.* 2019; 73: e51–e65.

17. 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 Oct 6;7(1):e574.

18. Practice Guidelines for Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration: Application to Healthy Patients Undergoing Elective Procedures: An Updated Report by the American Society of Anesthesiologists Task Force on Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration. Anesthesiology. 2017 Mar;126(3):376-393.

19. Gavin Lloyd et al. Procedural sedation in Emergency Medicine. 2020 March 11. Retrieved from:https://www.rcemlearning.co.uk/reference/procedural-sedation-emergency-medicine-2018/#1571048557784-2beccfa4-414c

20. Apfelbaum J, Gross J, Connis R, Agarkar M, Arnold D, Coté C, Tung A. 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: 437–79.

21. Ferguson I, Bell A, Treston G, New L, Ding M, Holdgate A. Propofol or ketofol for procedural sedation and analgesia in emergency medicine-The POKER study: a randomized double-blind clinical trial. *Ann. Emerg. Med.*2016; 68: 574–82.e571.

22. Miller KA, Andolfatto G, Miner JR, Burton JH, Krauss BS. Clinical practice guideline for emergency department procedural sedation with propofol: 2018 update. Annals of emergency medicine. 2019 May 1;73(5):470-80.

23. Vuyk Jaap, Sitsen Elske, Reekers Marije. Intravenous Anesthetics *Miller's Anesthesia*. 9 Philadelphia: Elsevier; theed. 2019; 638–79.

24. Conrardy M, LaPlant W. (2019, Nov 11). Procedural Sedation. [NUEM Blog. Expert Commentary by Trueger S]. Retrieved from http://www.nuemblog.com/blog/procedural-sedation.

25. Barr J, Fraser GL, Puntillo K, et al. Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit. Crit Care Med, 2013; 41:263.

26. Lexicomp Online. Copyright © 1978-2022 Lexicomp, Inc. All Rights Reserved.

27. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 2018; 46:e825.

28. Robert L Frank, MD, FACEP Procedural sedation in adults outside the operating room Aug 17, 2021. fromhttps://www-uptodate-com.ezproxy.dbazes.lsmuni.lt/contents/procedural-sedation-in-adults-outside-the-operating-room

29. Miner JR, Burton JH. Clinical practice advisory: Emergency department procedural sedation with propofol, Ann Emerg Med. 2007;50(2):182. Epub 2007 Feb 23.

30. Jalota L, Kalira V, George E, Shi YY, Hornuss C, Radke O, Pace NL, Apfel CC, Perioperative Clinical Research Core BMJ. 2011;342:d1110. Epub 2011 Mar 15.

31. Willman EV, Andolfatto G, A prospective evaluation of "ketofol" (ketamine/propofol combination) for procedural sedation and analgesia in the emergency department. Ann Emerg Med. 2007;49(1):23. Epub 2006 Oct 23.

32. Hig CC, Jr, McLeskey CH, Nahrwold ML, et al. Hemodynamic effects of propofol: data from over 25,000 patients. *Anesth Analg.* 1993;77:S21–S29

33. Neuman G, Koren G. Safety of procedural sedation in pregnancy. Journal of Obstetrics and Gynecology Canada. 2013 Feb 1;35(2):168-73.

34. Hinkelbein, Jochen; Lamperti, Massimo; Akeson, Jonas; Santos, Joao; Costa, Joao; De Robertis, Edoardo; Longrois, Dan; Novak-Jankovic, Vesna; Petrini, Flavia; Struys, Michel M.R.F.; Veyckemans, Francis; Fuchs-Buder, Thomas*; Fitzgerald, Robert† European Society of Anaesthesiology and European Board of Anaesthesiology guidelines for procedural sedation and analgesia in adults, European Journal of Anaesthesiology: January 2018 - Volume 35 - Issue 1 - p 6-24

35. Yap CYL, Taylor DM, Kong DCM, Knott JC, Taylor SE; Sedation for Acute Agitation in Emergency Department Patients: Targeting Adverse Events (SIESTA) Collaborative Study Group. Risk Factors for Sedation-related Events During Acute Agitation Management in the Emergency Department. Acad Emerg Med. 2019 Oct;26(10):1135-1143.

36. Bellagio MF et al. 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.

37. Prakash, Amit; Webb, Stephen T. Procedural sedation and analgesia for adults in Europe, European Journal of Anaesthesiology: January 2018 - Volume 35 - Issue 1 - p 4-5

38. Dowling, Laura P., "Aldrete Discharge Scoring: Appropriate for Post Anesthesia Phase I Discharge?" (2015). Master's Theses and Capstones. 14.

39. Barbic D, Andolfatto G, Grunau B, Scheuermeyer FX, Macewan B, Qian H, Wong H, Barbic SP, Honer WG. Rapid Agitation Control With Ketamine in the Emergency Department: A Blinded, Randomized Controlled Trial. Ann Emerg Med. 2021 Dec;78(6):788-795.

40. Schick A, Driver B, Moore JC, Fagerstrom E, Miner JR. Randomized Clinical Trial Comparing Procedural Amnesia and Respiratory Depression Between Moderate and Deep Sedation With Propofol in the Emergency Department. Acad Emerg Med. 2019 Apr;26(4):364-374.

41. Yap CYL, Taylor DM, Kong DCM, Knott JC, Taylor SE; Sedation for Acute Agitation in Emergency Department Patients: Targeting Adverse Events (SIESTA) Collaborative Study Group. Risk Factors for Sedation-related Events During Acute Agitation Management in the Emergency Department. Acad Emerg Med. 2019 Oct;26(10):1135-1143.

42. Hayes J, Matava C, Pehora C, El-Beheiry H, Jarvis S, Finkelstein Y. Determination of the median effective dose of propofol in combination with different doses of ketamine during gastro-duodenoscopy in children: a randomized controlled trial. Br J Anaesth. 2018 Aug;121(2):453-461.

43. Lemoel F, Contenti J, Giolito D, Boiffier M, Rapp J, Istria J, Fournier M, Ageron FX, Levraut J. Adverse Events With Ketamine Versus Ketofol for Procedural Sedation on Adults: A Double-blind, Randomized Controlled Trial. Acad Emerg Med. 2017 Dec;24(12):1441-1449.

44. Bowers KJ, McAllister KB, Ray M, Heitz C. Ketamine as an Adjunct to Opioids for Acute Pain in the Emergency Department: A Randomized Controlled Trial. Acad Emerg Med. 2017 Jun;24(6):676-685.

45. Rubinstein O, Barkan S, Breitbart R, Berkovitch S, Toledano M, Weiser G, Karadi N, Nassi A, Kozer E. Efficacy of oral ketamine compared to midazolam for sedation of children undergoing laceration repair: A double-blind, randomized, controlled trial. Medicine (Baltimore). 2016 Jun;95(26):e3984.

46. Reynolds SL, Bryant KK, Studnek JR, Hogg M, Dunn C, Templin MA, Moore CG, Young JR, Walker KR, Runyon MS. Randomized Controlled Feasibility Trial of Intranasal Ketamine Compared to Intranasal Fentanyl for Analgesia in Children with Suspected Extremity Fractures. Acad Emerg Med. 2017 Dec;24(12):1430-1440.

47. Smischney NJ, Nicholson WT, Brown DR, Gallo De Moraes A, Hoskote SS, Pickering B, Oeckler RA, Iyer VN, Gajic O, Schroeder DR, Bauer PR. Ketamine/propofol admixture vs etomidate for intubation in the critically ill: KEEP PACE Randomized clinical trial. J Trauma Acute Care Surg. 2019 Oct;87(4):883-891.

48. Lee JS, Jeon WC, Park EJ, Min YG, Jung YS, Kim GW, Choi SC. Adjunctive atropine versus metoclopramide: can we reduce ketamine-associated vomiting in young children? a prospective, randomized, open, controlled study. Acad Emerg Med. 2012 Oct;19(10):1128-33.

49. Graudins A, Meek R, Egerton-Warburton D, Oakley E, Seith R. The PICHFORK (Pain in Children Fentanyl or Ketamine) trial: a randomized controlled trial comparing intranasal ketamine and fentanyl for the relief of moderate to severe pain in children with limb injuries. Ann Emerg Med. 2015 Mar;65(3):248-254.e1. doi: 10.1016/j.annemergmed.2014.09.024. Epub 2014 Nov 18. PMID: 25447557.

50. Andolfatto G, Abu-Laban RB, Zed PJ, Staniforth SM, 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 Jun;59(6):504-12.e1-2.

51. Sanri E, Karacabey S, Akoglu H, Kaya B, Guneysel O. Comparison of ketamine/propofol (ketofol) and etomidate/fentanyl (etofen) combinations for procedural sedation and analgesia in the emergency department: An observational study. Turk J Emerg Med. 2017 Mar 19;17(3):89-94

52. Walravens S, Buylaert W, Steen E, De Paepe P. Implementation of a protocol using ketamine-propofol ('ketofol') in a 1 to 4 ratio for procedural sedation in adults at a university hospital emergency department - report on safety and effectiveness. Acta Clin Belg. 2021 Oct;76(5):359-364

53. Jalili S, Esmaeeili A, Kamali K, Rashtchi V. Comparison of effects of propofol and ketofol (Ketamine-Propofol mixture) on emergence agitation in children undergoing tonsillectomy. Afr Health Sci. 2019 Mar;19(1):1736-1744.

54. Smithburger PL, Patel MK. Pharmacologic Considerations Surrounding Sedation, Delirium, and Sleep in Critically Ill Adults: A Narrative Review. J Pharm Pract. 2019 Jun;32(3):271-291

55. Heim M, Draheim R, Krupp A, Breihan P, O'Rourke A, Wells J, Fish J. Evaluation of a Multidisciplinary Pain, Agitation, and Delirium Guideline in Mechanically Ventilated Critically Ill Adults. Hosp Pharm. 2019 Apr;54(2):119-124.

56. Zhang Q, Yu Y, Lu Y, Yue H. Systematic review and meta-analysis of propofol versus barbiturates for controlling refractory status epilepticus. BMC Neurol. 2019 Apr 06;19(1):55.

57. Short SM, Aun CS. Haemodynamic effects of propofol in children. Anesthesia. 1991;46:783–785

58. Bassett KE, Anderson JL, et al. Propofol for procedural sedation in children in the emergency department. *Ann Emerg Med.* 2003;42:773–782.

59. Ghadami Yazdi A, Ayatollahi V, Hashemi A, Behdad Sh, Ghadami Yazdi E. Effect of two Different Concentrations of Propofol and Ketamine Combinations (Ketofol) in Pediatric Patients under Lumbar Puncture or Bone Marrow Aspiration. Iran J Ped Hematol Oncol. 2013;3(1):187-92. Epub 2013 Jan 22.