J Pediatr (Rio J). 2017;93(s1):2–18

Jornal de Pediatria
www.jped.com.br

REVIEW ARTICLE

Sedation and analgesia for procedures in the pediatric emergency room☆,☆☆

Carlos Eduardo Ramalho[a,b], Pedro Messeder Caldeira Bretas[a,b], Claudio Schvartsman[b,c], Amélia Gorete Reis[a,b,*]

[a] Universidade de São Paulo (USP), Faculdade de Medicina, Hospital das Clínicas, Instituto da Criança, São Paulo, SP, Brazil
[b] Universidade de São Paulo (USP), Faculdade de Medicina, Departamento de Pediatria, São Paulo, SP, Brazil
[c] Faculdade Israelita de Ciências da Saúde Albert Einstein, São Paulo, SP, Brazil

Received 4 May 2017; accepted 26 May 2017
Available online 23 September 2017

KEYWORDS
Conscious sedation;
Deep sedation;
Analgesia;
Child;
Emergency service;
Emergency medicine

Abstract
Objective: Children and adolescents often require sedation and analgesia in emergency situations. With the emergence of new therapeutic options, the obsolescence of others, and recent discoveries regarding already known drugs, it became necessary to review the literature in this area.
Data sources: Non-systematic review in the PubMed database of studies published up to December 2016, including original articles, review articles, systematic reviews, and meta-analyses. References from textbooks, publications from regulatory agencies, and articles cited in reviews and meta-analyses through active search were also included.
Data synthesis: Based on current literature, the concepts of sedation and analgesia, the necessary care with the patient before, during, and after sedoanalgesia, and indications related to the appropriate choice of drugs according to the procedure to be performed and their safety profiles are presented.
Conclusions: The use of sedoanalgesia protocols in procedures in the pediatric emergency room should guide the professional in the choice of medication, the appropriate material, and in the evaluation of discharge criteria, thus assuring quality in care.

☆ Please cite this article as: Ramalho CE, Bretas PM, Schvartsman C, Reis AG. Sedation and analgesia for procedures in the pediatric emergency room. J Pediatr (Rio J). 2017;93:2–18.
☆☆ Study carried out at Universidade de São Paulo (USP), Faculdade de Medicina, Hospital das Clínicas, Instituto da Criança, São Paulo, SP, Brazil.
* Corresponding author.
E-mail: ameliareis30@gmail.com (A.G. Reis).

http://dx.doi.org/10.1016/j.jped.2017.07.009

PALAVRAS-CHAVE
Sedação consciente;
Sedação profunda;
Analgesia;
Criança;
Serviço de emergência;
Medicamento de emergência

Sedação e analgesia para procedimentos no pronto-socorro de pediatria

Resumo
Objetivo: Crianças e adolescentes necessitam frequentemente de sedação e analgesia em situações de emergência. Com o surgimento de novas opções terapêuticas, a obsolescência de outras e descobertas recentes das drogas já conhecidas, fez-se necessário uma nova revisão da literatura nesta área.
Fontes dos dados: Revisão não sistemática na base de dados PubMed de estudos publicados até dezembro de 2016, incluindo artigos originais, artigos de revisão, revisões sistemáticas e meta-análises. Também foram incluídos referências de livros-texto, publicações de agências reguladoras além de artigos citados nas revisões e meta-análises através de busca ativa.
Síntese dos dados: Com base na literatura atual, são apresentados os conceitos de sedação e analgesia, os cuidados necessários com o paciente antes, durante e após a sedoanalgesia, além de indicações quanto à escolha apropriada dos fármacos de acordo com o procedimento a ser realizado e o perfil de segurança destes.
Conclusões: O emprego de protocolos de sedoanalgesia em procedimentos no Pronto-Socorro pediátrico deve orientar o profissional na escolha da medicação, do material adequado e na avaliação dos critérios de alta, garantindo assim qualidade na assistência.

Introduction

Children and adolescents often require sedation and analgesia when treated in an emergency situation. Invasive and noninvasive procedures are part of diagnostic and therapeutic techniques in pediatrics, and are often uncomfortable for the child, the parents, and health professionals.[1] Although necessary, sedation and analgesia may have adverse effects, requiring management in an adequate environment and performed by trained professionals.[2]

Sedation for procedures has advanced and expanded in the last decades; no longer the exclusive scope of anesthesiology, now it is being routinely used by the most varied of medical specialties, such as gastroenterology, cardiology, neurology, radiology, emergency medicine, and pediatric intensive care.[3] In a qualitative study with physicians from Ireland and the United Kingdom, McCoy et al. identified the lack of training and education in this area as a significant barrier. The standardization of sedation practices and standardization of guidelines and recommendations remains a challenge.[4] In Brazil, few review articles have been published on this topic in recent years[5,6]; protocols are suggested in two of them.[6,7]

Sedation reduces the state of consciousness, while analgesia reduces or eliminates the perception of pain. Many analgesics have some sedative effect, but few sedatives have the property of analgesia. The aim of sedation in pediatrics differs from that in adult patients, as it is administered to control behavior and allow safe completion of the procedure.[2] For cooperative children, non-pharmacological modalities should be considered, such as parental presence, hypnosis, distraction, and topical anesthetics, as they may reduce the need for or depth of pharmacological sedation.[8,9]

Levels of sedation

Sedation is described as a continuum, represented by progressive stages, from mild to general anesthesia. Ketamine, as an exception, is a dissociative agent that has the particularity of producing a sedation that does not follow this pattern; the effect is present or absent, with maintenance of spontaneous breathing, protective reflexes, and cardiovascular stability.[10]

In 2002, the American Society of Anesthesiologists (ASA) defined the four levels of sedation[11]:

- Minimal sedation (anxiolysis): a state induced by medication in which patients respond normally to verbal commands. Although cognitive function and coordination may be impaired, ventilatory and cardiovascular functions are not affected.
- Moderate sedation: also called ''conscious sedation,'' it is a state of drug-induced decrease in consciousness, in which the patient responds purposefully to verbal commands, isolated or accompanied by light tactile stimuli. No intervention is necessary to maintain airway patency and spontaneous ventilation is adequate. In general, cardiovascular function is usually maintained.
- Deep sedation: a drug-induced decrease in consciousness from which patients cannot be easily awakened, but respond to repeated or painful stimuli. The ability to independently maintain ventilatory function may be impaired. Patients may need assistance to maintain airway patency and spontaneous ventilation may be inadequate. Cardiovascular function is generally maintained.
- General anesthesia: a state of drug-induced loss of consciousness from which patients are not aroused, even with painful stimuli. The ability to maintain ventilatory

Table 1 Neonatal Infant Pain Scale (NIPS).

Variable	0 points	1 point	2 points
Facial expression	Relaxed	Grimacing	–
Crying	Not crying	Whimpering	Vigorous
Breathing	Regular	Different from basal	–
Arms	Relaxed	Flexed/extended	–
Legs	Relaxed	Flexed/extended	–
State of alertness	Sleeping and/or peaceful	Restless and/or fussy	–

Presence of pain: score > 3. Adapted from Lawrence et al.[15]

Table 2 Face, Legs, Activity, Cry, and Consolability (FLACC) scale.

Categories	0 points	1 point	2 points
Face	No particular expression or smile	Occasional grimace or frown; withdrawn, uninterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs; frequent complains
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to; distractible	Difficult to console or comfort

Adapted from Merkel et al.[16]

function is impaired and patients generally need assistance to maintain airway patency and positive pressure ventilation. Cardiovascular function may be impaired.

One of the important aspects of pain relief in pediatrics implies the understanding of pain assessment methods and their use. Pain can be assessed in children using physiological parameters, behavioral observation, and self-report. The patient with pain will have tachycardia, pupillary dilatation, sweating, and peripheral vasoconstriction.[12,13] No pain assessment should be based solely on these parameters, but rather should be made in combination with validated scales for their adequate measurement. Pain assessment scales have been validated for use in pediatrics, considering the child's developmental phase (verbal or pre-verbal age) and their cognitive ability to report pain.[14]

The Neonatal Infant Pain Scale (NIPS) was developed to evaluate the pain response of patients in the neonatal period, assessing six objective parameters (Table 1).[15] The Face, Legs, Activity, Cry, and Consolability (FLACC) scale is validated for children between 2 months and 7 years, and scores five reactions to pain on a scale from 0 to 2 (Table 2).[16,17] In smaller children, picture-based face are easy to use because they do not require numerical knowledge or certain words (Figs. 1–3).[18–20] Children older than 8 years are already cognitively able to use visual analog scales (Fig. 4).[21]

Sedation and analgesia for procedures should lead to a state of decreased level of consciousness that allows the patient to maintain airway patency independently and

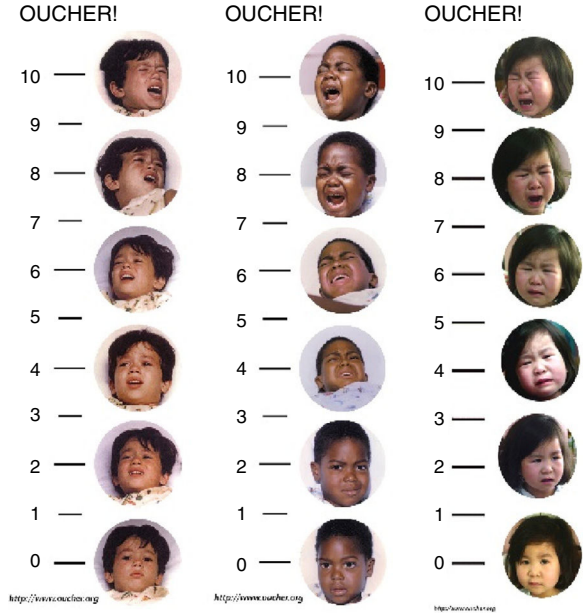

Figure 1 OUCHER scale. Adapted from OUCHER.[18] Explain to the child to score that the intensity of the pain increases in the scale from the bottom up and ask her to point to the figure that demonstrates the intensity of pain she is feeling at the moment.

continuously. For this purpose, the correct choice of drugs, doses, and forms of administration are important. Younger and severely ill children often require deeper sedation for painful procedures.

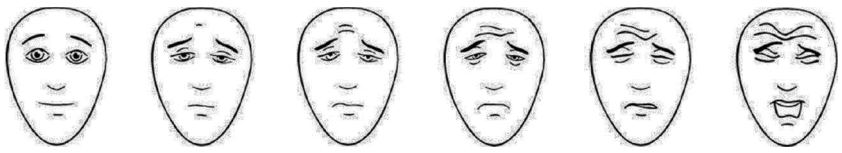

Figure 2 Faces Pain scale – Revised. Adapted from Faces Pain Scale – Revised © 2001, International Association for the Study of Pain (www.iasp-pain.org/FPSR). Used with permission. Explain to the child to score the chosen face as 0, 2, 4, 6, 8, or 10, counting from left to right; 0 = no pain and 10 = a great deal of pain. Do not use words like ''happy'' or ''sad.'' This scale aims to measure how children feel internally and not how they appear to be.

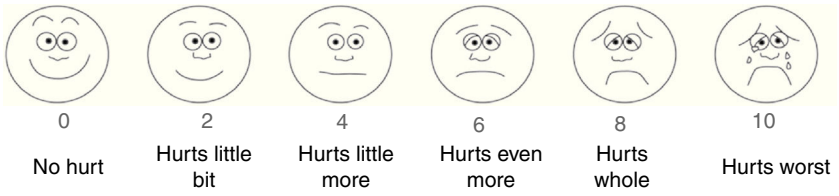

Figure 3 Wong-Baker pain rating scale. Adapted from © 1983 Wong-Baker FACES Foundation. www.WongBakerFACES.org. Use with permission. Explain to the child that each face represents a person with none to a lot of pain. Ask her to choose the face that best translates the pain she is experiencing.

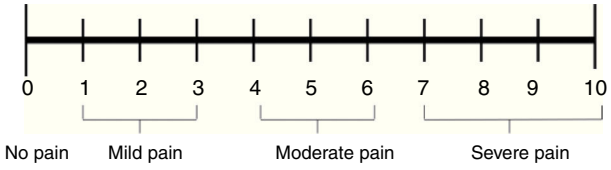

Figure 4 Visual analog scale. Adapted from McCaffery et al.[21] Simple numerical scale. Ask the patient to indicate the intensity of the current, the best and the worst level of pain in the last 24 h on a scale of 0 (no pain) to 10 (worst pain imaginable).

Pre-sedation assessment

The American Society of Anesthesiologists (ASA) recommends the classification of patients into six categories, according to their baseline health (Table 3). Patients classified as ASA I and II are suitable candidates for minimum, moderate, or deep sedation, whereas ASA III and IV patients, those with special needs or anatomic airway abnormalities, require additional considerations, implying moderate or deep sedation.[11] Through the mnemonic acronym ''SAMPLE'' it is possible to recall the essential components of the patient's medical history that should be considered for sedation assessment (Table 4).

Adverse events of the airway, cardiovascular system, and respiratory system are the main causes of morbidity and mortality associated with sedoanalgesia in the pediatric population.[22] A meta-analysis (2016) including 41 studies with 13,883 procedures under sedation in children identified vomiting, restlessness, hypoxia, and apnea as the most frequent complications. In that study, the incidence of severe respiratory adverse events (laryngospasm and need for intubation) was less than 0.5% and respiratory depression occurred in 1.5% of the sedations, with no reports of bronchoaspiration; 97% of laryngospasm cases were associated with the use of ketamine.[23] Cravero et al. published a multicenter study reporting even lower rates of adverse events, with an incidence of laryngospasm and aspiration of 0.3 and 4.3 per 10,000 cases, respectively.[24] A meta-analysis of 9652 adults undergoing sedation for procedures also found an incidence of adverse reactions similar to that observed in the pediatric population.[25]

Sedative agents have the potential to impair airway protective reflexes, particularly during deep sedation, with the risk of pulmonary aspiration representing one of the

Table 3 Classification of the patient's baseline health status, according to the American Society of Anesthesiologists.

Class	Health status
I	A normal healthy patient
II	A patient with mild systemic disease
III	A patient with severe systemic disease
IV	A patient with severe systemic disease that is a constant threat to life
V	A moribund patient who is not expected to survive without the operation
VI	A patient declared brain-dead whose organs are being removed for donor purposes

Table 4 Brief and systematic evaluation of the patient submitted to sedation (''SAMPLE'').

Letter	Assessed item
S	**S**igns and symptoms of current pathology
A	**A**llergy to medication, food, or latex
M	**M**edication being taken, whether continuous or not
P	**P**ast medical history – comorbidities, previous complications related to sedative agents
L	**L**iquids and solids – fasting time and which type of food ingested
E	**E**vents related to the need for sedation

Table 5 Adequate fasting time for sedation, according to the American Society of Anesthesiologists.

Type of food	Fasting time
Clear liquids[a]	2 h
Breast milk	4 h
Infant formula and nonhuman milk	6 h
Light meal (toast and liquids)	6 h

[a] Water, fruit juice without pulp, carbonated drinks, light tea, and black coffee.

reasons to proceed with caution and evaluate the time of fasting before performing a procedure (Table 5). The 2011 ASA recommendations are based on the extrapolation of patients submitted to general anesthesia at the surgical center, not consistent with the reality of sedoanalgesia at the emergency room.[26] As of 2014, the American College of Emergency Physicians (ACEP) started to recommend that sedation for procedures should not be delayed according to the time of fasting, because there is no evidence that it is related to a reduction in the risk of aspiration or vomiting.[27–29] Clark et al. demonstrated that patients with shorter fasting times submitted to deep sedation for elective procedures outside the surgical room experienced similar complication rates when compared to those with longer fasting duration.[30] Despite ACEP's current recommendations, the authors of this article believe that the risk of sedation and the possibility of aspiration should be weighed against the potential benefits of the procedure, since the number of studies in pediatric emergency units is very small.

When performing the physical examination, special attention should be given to cardiac, pulmonary, renal, hepatic, and genetic abnormalities that may alter the child's expected response to analgesic and sedative medications.[31–34] Some authors have shown an increased risk of adverse events associated with sedation of patients with comorbidities (ASA > 1).[32–34] Airway examination should be thorough, with an active search for characteristics that increase the risk of airway obstruction during the procedure, such as micrognathia, macroglossia, significant tonsil hypertrophy, limited airway opening, extreme obesity, short neck, excessive secretion, or decreased airway protective reflexes.[11] Some genetic and congenital diseases that occur with craniofacial malformations require a more cautious approach due to the difficult airway[35] (Table 6).

Table 6 Genetic and congenital diseases associated with difficult airway.

Cleft lip and palate
Trisomy of chromosome 21
Fibrodysplasia ossificans progressiva Mucopolysaccharidosis
Vascular malformations
Pierre Robin syndrome
Crouzon syndrome (craniofacial dysostosis)
Treacher Collins syndrome (mandibulofacial dysostosis)
Goldenhar's syndrome (hemifacial microsomia)
Klippel-Feil syndrome
Freeman-Sheldon syndrome (cranio-carpo-tarsal dysplasia)

Source: Butler et al.[31]

In a retrospective study with 11,219 children undergoing general anesthesia procedures with tracheal intubation, laryngoscopy was considered difficult in 1.35% of the cases, with a higher rate in children younger than 1 year of age when compared with those older than 1 year, with an incidence of 4.7% and 0.7%, respectively. A higher risk of difficult laryngoscopy was also identified in patients classified as ASA III and IV, with low body mass index (BMI), submitted to oral cavity, maxillofacial, and cardiac surgery.[36] A similar study analyzed a cohort of 102,305 cases of adult patients submitted to general anesthesia and found a difficult laryngoscopy incidence of 4.9%, three-fold that of the general pediatric population.[37]

Patient vital signs should be recorded prior to the start of sedation, after each medication dose, at regular intervals during the procedure, at the end, during the recovery phase, and at hospital discharge.[11] The American Academy of Pediatrics (AAP) recommends that vital signs should be recorded every ten minutes in patients submitted to moderate sedation and every five minutes for those under deep sedation.[38]

Excluding the minimal sedation, where the observation of the level of consciousness is sufficient, patient monitoring must be continuous and include a pulse oximeter, cardiac, respiratory, and blood pressure monitor.[38] Capnography can be used in association with the pulse oximeter, being capable of detecting apnea before the latter; it is recommended in moderate sedation and is mandatory in deep sedation.[11,27,38]

A meta-analysis from 2011, based on studies with adult patients submitted to sedation for procedures, identified a 17.6-fold greater probability of detecting respiratory depression when monitoring with capnography.[39] Langhan et al. randomized 154 children submitted to sedation in the emergency department and found that patients monitored with capnography had earlier interventions in hypoventilation episodes, leading to a lower number of episodes of decreased oxygen saturation in relation to the control group.[40]

Special care should be taken when covering the face and trunk of the child, since the observation of mucosal color and rib cage movement becomes impaired. In other situations of impaired observation, such as magnetic resonance imaging (MRI), continuous non-invasive monitoring equipment (cardiac monitor, oximeter, capnography) should be used. In addition to adequate sources and routes to supply oxygen and suction material, it is mandatory to always have an emergency cart at hand with a defibrillator, resuscitation drugs, antidotes, and equipment for difficult airways.[11]

The presence of a trained professional who knows how to recognize airway impairment and intervene to provide ventilatory support is essential.[41] The AAP recommends that one professional be present for patient monitoring and another with training in airway management and suctioning, bag-mask ventilation, vascular access, and cardiopulmonary resuscitation, both with advanced life support training in pediatrics.[38] A study of the Pediatric Sedation Research Consortium analyzed data from 131,751 cases of pediatric patient sedation for procedures in hospitals in the United States, observing that there was no statistical difference in rates of severe adverse events when sedation was performed by different specialists.[42] The training of professionals involved in this type of practice is important to

Table 7 Steps for sedation and analgesia.

Anamnesis	Physical examination	Monitoring	Discharge criteria
Signs and symptoms **A**llergy **M**edication **P**ast medical history **L**iquids and solids **E**vents	• Upper airway: mouth opening, jaw size • Neck flexion: ability to pull the chin to the chest (assess limitation), not applicable for victims with spinal cord trauma • Respiratory auscultation • Heart auscultation • Distal perfusion: pulse, skin temperature, capillary perfusion	• Heart rate and electrocardiogram tracing • Respiratory frequency • Blood pressure • Pulse oximetry • Level of consciousness • Pain scale • Capnography (moderate and deep sedation)	• Airway, vital signs and stable pulse oximetry and back to basal level • Able to obey commands appropriate for age • Hydrated patient and tolerating oral fluid intake • Awakened patient and at his/her basal level of verbal ability • Patient able to sit unassisted (if appropriate for age)

decrease adverse events and promote better patient comfort and safety, and can be carried out using traditional models or through simulations.[43–47]

One of the periods of greatest risk related to sedation is the recovery phase, so monitoring during this period is mandatory. Patients should be eligible for discharge if they wake up easily, talk and sit unaided, are able to follow age-appropriate commands, are hydrated, and show stable cardiovascular function and patent airways. For very young children or those with some cognitive disorder, with difficulty in interaction, the return to the level of pre-sedation responsiveness must be sought.[38] The time of recovery to the baseline state varies with the drug and dose used, but most patients can be discharged after 1–2 h. It is recommended that patients not be submitted to activities that require concentration or motor skills in the first hours after recovery from sedation. Caregivers should be instructed to report any adverse events that occur within 24 h of discharge.[41]

Protocols for sedation and analgesia in the emergency room are essential. The implementation of a specific procedure sedation protocol in a Canadian tertiary hospital reduced the median time between sedation administration and discontinuation of patient monitoring from 49 to 19 min, releasing important resources in a high-demand emergency department[48] (Table 7).

Therapeutic arsenal

The choice of medication used during the sedation and analgesia process should consider the criteria related to the procedure to which the patient will be submitted, as well as the criteria related to the baseline state and comorbidities. Table 8 shows the suggested medications for different types of procedure. The main drugs used in the pediatric emergency unit will be described below. Table 9, at the end of the chapter, summarizes the different characteristics of each drug.

Benzodiazepines

Benzodiazepines are hypnotic sedative agents. Their mechanism of action occurs through their inhibitory effect on the central nervous system (CNS). They bind to postsynaptic gamma-aminobutyric acid (GABA) receptors and increase the permeability to chlorine ions, leading to hyperpolarization and stabilization of the neuronal membrane. They have hepatic metabolism and renal excretion. Their pharmacological effects are sedation, hypnosis, anxiety reduction, amnesia, muscle relaxation, and anticonvulsant effects. This group does not have an analgesic effect and should be associated with other agents, such as opioids, if they are used in painful procedures.[49] The two main drugs of the group used for sedation in procedures are diazepam and midazolam.

Diazepam has been widely used for sedation, but may cause prolonged sedation because it has a long and variable half-life. Its use has been replaced by midazolam, which was introduced to the market due to its varied routes of administration and shorter duration.[1] Wright et al., in a prospective, multicenter, randomized study, compared diazepam and midazolam for sedation in emergency department procedures, observing that patients receiving midazolam achieved higher levels of early sedation, higher 90-minute score on the alertness scale, less need for a new dose during the procedure, and less pain during infusion.[50]

Midazolam

Midazolam is the most commonly used intravenous sedative in the emergency department for adults and children. Ilkhanipour et al. carried out a survey in 80 emergency residence programs in the United States and found a 82% rate of institutions using midazolam as the drug of choice for sedation of pediatric patients in the emergency department.[51] A study conducted in Brazil by Sukys et al. in a pediatric emergency unit found that midazolam was the sedative of choice in 80% of rapid intubation sequences.[52] The rationale for this fact is the rapid action onset, short duration, anterograde amnesia, and a wide variety of administration routes.

Midazolam is metabolized by cytochrome p450; therefore, the first passage effect should be considered depending on the route of administration; additionally, its metabolization may be compromised in the presence of inflammatory processes, hypoxemia, or use of other drugs metabolized by the same route. It has high protein affinity (97%), thus, in the presence of other medications with the same characteristic, there is an increase in the free fraction of circulating midazolam. Its elimination is 80% by the

Table 8 Sedoanalgesia for emergency procedures.

Type of procedure	Indications	Desired effect	Suggestion
Non-invasive procedures	Computed tomography Echocardiogram Electroencephalogram Ultrasonography	Motor control	Comfort measures Midazolam[a] Dexmedetomidine
Procedures associated with light pain and high degree of anxiety	Tracheostomy exchange Gastrostomy exchange Dental procedures Nasofibroscopy Peripheral venous puncture Suture Lumbar puncture	Analgesia Sedation Motor control Reduction of anxiety	Comfort measures Midazolam[b] Ketamine Topical or local analgesia
Procedures associated with high level of pain, high level of anxiety, or both	Abscess drainage Arthrocentesis Bone marrow aspiration Pericardial puncture Cardioversion Central venous puncture Burn debridement Reduction of fractures Hernia reduction Paraphimosis reduction Thoracentesis Thoracic drainage Paracentesis Physical examination of victims of sexual violence	Sedation Analgesia Motor control Reduction of anxiety Amnesia	Fentanyl Midazolam + Fentanyl Ketamine Ketamine + Propofol Propofol + Fentanyl Morphine

[a] Midazolam for EEG is not a good alternative.
[b] Consider association with analgesics, depending on the procedure.

renal route.[49] Due to these pharmacological characteristics, it should be administered with caution in patients with hepatopathies and nephropathies. The half-life of midazolam may also be increased in neonates, due to the immaturity of kidney and liver function.[53]

It can be administered through the oral (PO), rectal (RR), intranasal (IN), intramuscular (IM), and intravenous (IV) routes. The IV presentation (5 mg/mL) may be used in any route of administration, but it has an irritant effect on the mucosa.[54] The oral presentation has a lower concentration (2 mg/mL), being more palatable, which results in a better acceptance by the patients according to specialists.[55] Smith et al., in a randomized study with 77 pediatric patients, observed less discomfort when atomized IN lidocaine at 4% was used as a premedication.[56] Chiaretti et al., in a study of 46 children submitted to sedation for non-painful procedures, found no discomfort or pain related to the use of IN midazolam when in combination with lidocaine spray as a premedication.[57]

The main side effects are hypotension, respiratory depression, and paradoxical effect. Midazolam reduces peripheral vascular resistance and the action of the sympathetic nervous system, which decreases the cardiac output, with implications mainly in hypovolemic patients or in those with cyanotic heart diseases. Respiratory depression is dose-dependent. In combination with opioids, there is a greater risk of hypotension and respiratory depression; on the other hand, the paradoxical effect is reduced in this association.[1,58]

Flumazenil

Flumazenil is a central-action benzodiazepine antagonist and its administration is exclusively by the intravenous route. Reversal of benzodiazepine effects is contrary to its appearance during sedation, *i.e.*, small doses of midazolam are necessary to generate an anxiolytic effect, while higher doses of flumazenil are necessary to reverse this effect. In turn, high doses of midazolam are required to induce deep sedation, while small doses of flumazenil reverse this effect. Side effects are elevated intracranial pressure and decreased convulsive threshold, so it should be used with caution in patients taking medications that may induce seizures (tricyclic antidepressants, cocaine, lithium, methylxanthines, isoniazid, monoamine oxidase inhibitors, bupropion, theophylline).[59]

Opioids

Opioids modulate the cortical perception of pain. They act by binding to central and peripheral μ, δ, and κ receptors,

Table 9 Pharmacological characteristics of drugs used in sedation and analgesia.

Drug	Effects	Side effects	Indications	Dose	Onset of action	Duration of action
Sedative-hypnotic						
Midazolam	Sedation, motor control, anxiety reduction, no analgesic effect	Hypotension, respiratory depression, paradoxical effect	Procedures that require sedation, Reduced anxiety or amnesia	IV (age 6 months–5 years): initial 0.05–0.1 mg/kg, maximum of 0.6 mg/kg IV (6–12 years): initial 0.025–0.05 mg/kg, maximum of 0.4 mg/kg IM: 0.1–0.15 mg/kg PO: 0.5–0.75 mg/kg IN: 0.2–0.5 mg/kg RR: 0.25–0.5 mg/kg	2–3 min 2–3 min 10–20 min 15–30 min 10–15 min 10–30 min	45–60 min 45–60 min 60–120 min 60–90 min 60 min 60–90 min
Diazepam	Sedation, motor control, anxiety reduction, no analgesic effect	Hypotension, respiratory depression, paradoxical effect	Seldom used due to long half-life	IV: initial 0.05–0.1 mg/kg, Max 0.25 mg/kg	2–3 min	45–60 min
Propofol	Fast and short sedation	May cause pain at infusion, hypotension, apnea and bradycardia	Short-term procedures, associated or unassociated with analgesics	IV: 1–2 mg/kg, may repeat 0.5 mg/kg every 3–5 min	1 min	5–15 min
Etomidate	Fast and short sedation	May cause local pain, myoclonus, transient adrenal suppression	Short-term procedures, associated or unassociated with analgesics	IV: 0.2–0.3 mg/kg	30–60 s	5–15 min
Dexmedetomidine	Sedation with respiratory drive maintenance Does not change EEG tracing Off-label use in pediatrics	May cause arrhythmia, hypotension, and hypertension	Imaging procedures (CT and MRI), endoscopy, EEG	IV: 2 mcg/kg IN/oral mucosa: 1–3 mcg/kg IM: 1–4.5 mcg/kg Oral: 5 mcg/kg	5–10 min	60–120 min

Table 9 (*Continued*)

Drug	Effects	Side effects	Indications	Dose	Onset of action	Duration of action
Analgesics						
Fentanyl	Analgesia	Bradycardia, chest stiffness, respiratory depression	Procedures with moderate to severe pain	IV: 1.0 μg/kg/dose, may be repeated every 3 min IN: 1.5 μg/kg/dose	2–3 min 2–5 min	30–60 min 30–60 min
Morphine	Analgesia	Release of histamine, hypotension, nausea, reduction of gastrointestinal motility	Procedures with moderate to severe pain	IV: initial 0.05–0.15 mg/kg, may be repeated every 5 min	5–10 min	30–60 min
Ketamine	Dissociative agent with analgesic and sedative properties	Laryngospasm, hypersalivation, emergency reactions, vomiting	Short-term painful procedures or when amnesia is desired	IV: 1–2 mg/kg, may repeat 0.5–1 mg/kg every 5–10 min IM: 2–5 mg/kg, may repeat 2–4 mg/kg after 10 min IN: 1–9 mg/kg	IV: 1 min IM: 3–5 min	IV: 15 min (dissociation), 60 min (recovery) IM: 15–30 min (dissociation), 90–150 min (recovery)
Antidotes						
Flumazenil	Benzodiazepine antagonist	Increased intracranial pressure, reduction of convulsive threshold	Reversal of unwanted effects	IV: 0.02 mg/kg/dose, may be repeated at each min up to a maximum of 1 mg	1–2 min	30–60 min
Naloxone	Opioid antagonist	Nausea, anxiety, sympathetic stimulation, hypertension, tachycardia, pulmonary edema, return of pain	Reversal of unwanted effects	IV or IM: 0.1 mg/kg/dose, maximum 2 mg/dose; can be repeated every 2 min if necessary[a]	IV: 2 min IM: 10–15 min	IV: 20–40 min IM: 60–90 min

IV, intravenous; IM, intramuscular; PO, oral route; IN, intranasal; RR, rectal route.
[a] The dose for partial reversal is lower: 0.01–0.03 mg/kg.

causing cellular hyperpolarization, reducing the release of neurotransmitters. Their main indication is for relief of moderate to severe pain.[12,13] Morphine and fentanyl are the most commonly used opioids in clinical practice.

Morphine

Morphine is an opioid with a delayed action onset (5–10 min) and prolonged duration (120–180 min). Delay in the clinical effect occurs because of its relatively low lipid solubility. It undergoes significant first passage metabolism and, therefore, oral doses should be six-fold greater than parenteral doses to achieve the same degree of analgesia.[60,61] It is indicated in procedures in which the aim is to maintain analgesia for a longer time, *e.g.*, in fracture fixation. Barcelos et al. compared morphine (0.1 mg/kg) and ketamine (2 mg/kg), both associated with midazolam (0.2 mg/kg), for analgesia in fracture reduction in 25 children in an emergency department, and found no statistical difference regarding failure rate, procedure start time, length of hospital stay, pain scales, or rate of satisfaction of parents and orthopedists.[62] Another recurrent use in clinical practice is the relief of acute or chronic intense pain, such as in patients with sickle-cell disease.[63]

The metabolism of morphine is hepatic and extrahepatic, with the metabolites being excreted in the urine. In patients younger than 6 months, the metabolization mechanisms are immature, and there is evidence of decreased clearance in children with cardiovascular instability.[61,64] McRorie et al. observed that children receiving IV morphine after cardiac surgery reached adult morphine clearance values at 6 months of age.[65] In another study, Lynn et al. identified adult morphine clearance values in infants around 1–3 months of age.[66] The variability of morphine duration is high, which makes it difficult to predict the duration of morphine effects.

Morphine stimulates the release of significant amounts of histamine and inhibits compensatory sympathetic responses. This effect can cause bronchoconstriction and is deleterious in asthmatics. Vasodilation produced by histamine may result in hypotension, especially with rapid infusion administration.[67]

Important gastrointestinal side effects are also observed with the use of morphine, such as nausea and vomiting that can occur in up to 40% of patients, an effect that tends to decrease with repeated doses of the medication. Another effect, which is common to all opioids, is increased tonus and reduced gastrointestinal motility.[67]

Discontinuation of morphine infusion is associated with abstinence phenomena. Signs and symptoms include pupillary dilation, tearing, sweating, shivers, hypertension, fever, vomiting, abdominal pain, diarrhea, muscle and joint pain, and behavioral changes.[68]

Fentanyl

Fentanyl is a synthetic opioid with approximately 100 times the analgesic power of morphine. It is highly liposoluble, which explains its rapid action onset. It has a half-life of 2–4 h on intermittent administration and 21 h after prolonged continuous infusion. This difference occurs due to the saturation of opioid receptors in the lipophilic peripheral tissues.[69,70]

The metabolism of fentanyl occurs almost exclusively in the liver; it has no active metabolites and a small fraction is excreted unaltered in the urine. Infants and young children have greater clearance than older children and adults, often requiring more frequent doses. Singleton et al. evaluated the plasma concentration of fentanyl in three different age groups and found a higher plasma concentration of fentanyl in adults compared to children, and an even lower concentration in infants.[71]

Some properties of fentanyl have clinical implications, for instance, changes in blood pH can alter its ionization and distribution between plasma and the CNS, and patients with acidosis may have an increase in the free fraction of fentanyl, putting them at higher risk of toxicity.[72]

Studies have shown that fentanyl administered by alternative routes is effective in relieving pain. Miner et al., in a randomized clinical trial of 41 children who received 1.5 mcg/kg of IV fentanyl or 3 mcg/kg of nebulized fentanyl, showed a similar result in the pain improvement score.[73] Borland et al., in a study comparing IN fentanyl at a dose of 1.7 mg/kg with IV morphine at a dose of 0.1 mg/kg, showed similar improvement in pain scores in the two groups of pediatric patients submitted to fracture reduction.[74] Similar results were achieved by Young et al. when comparing intranasal fentanyl (1 mcg/kg) with IM morphine (0.2 mg/kg) in fracture reduction in pediatric patients, and tolerance to administration was better in the IN fentanyl group.[75]

Fentanyl can cause hemodynamic impairment by bradycardia-induced decreased cardiac output.[58] A widely reported adverse effect, although rare, is chest wall stiffness, which is associated with high doses, above 5 mcg/kg with bolus administration.[60]

Respiratory depression is a side effect common to all opioids, and is associated with the administered dose. The incidence of respiratory depression is significantly higher when opioids are used in combination with benzodiazepines. Roback et al. analyzed the occurrence of side effects in 2500 patients who underwent sedation and analgesia in a pediatric emergency department in the United States, and found a rate of respiratory adverse events of 19.3% when there was an association between midazolam and fentanyl, and of 5.8% when midazolam was administered alone.[59,76]

The potential advantages of fentanyl over morphine for performing the procedure are: faster onset of action, shorter half-life, and avoidance of histamine release, with a low incidence of nausea, vomiting, and generalized pruritus. Additionally, there is no cross-reaction with morphine allergy.[77]

Naloxone

Naloxone is an opioid receptor antagonist. The most commonly used administration routes are IV and IM, but it can also be administered by the subcutaneous, sublingual, and endotracheal routes. The dose varies according to the desired effect, *i.e.*, partial reduction of the opioid effect (0.01–0.03 mg/kg) or complete reversal (0.1–2 mg/kg). After its administration, respiration return is observed in one to two minutes, and transient tachypnea may occur. Doses

may be repeated every two minutes if the expected effect is not achieved or the reversal has been transient, since the half-life of naloxone is lower than that of opioids.[78]

Possible side effects are nausea, anxiety, sympathetic stimulation, hypertension, tachycardia, pulmonary edema, and return of pain. At a low dose, naloxone seems to reduce the nausea caused by opioids. A meta-analysis carried out by Barrons and Woods concluded that the use of naloxone reduces the occurrence of postoperative nausea without significantly increasing the need for extra doses of opioids and without increasing pain scores; however, there was no decrease in the occurrence of vomiting.[79]

Ketamine

Ketamine is a dissociative anesthetic agent that acts on the N-methyl-D-aspartate-glutamate receptor, disconnecting the limbic and thalamocortical systems, dissociating the central nervous system from external stimuli. The cataleptic state allows potent analgesia, sedation, and amnesia, while maintaining airway patency, protective stimuli, and cardiovascular stability.[10]

It is widely used in painful short-term procedures or in those in which amnesia is desired, such as for the physical examination of patients that are victims of abuse.[80] It is not recommended for sedation in computed tomography (CT) of the skull or MRI, because the dissociative state can produce inappropriate movements, resulting in poorer image quality. It has hepatic metabolism and predominantly urinary excretion (91%).[10]

It is typically administered intravenously or intramuscularly, and may be administered by the intranasal and oral routes. The IV route allows faster recovery and less time until discharge, while the IM route is an independent predictor of emesis.[81,82] In a randomized study, the administration of higher doses of ketamine (1.5 and 2 mg/kg) compared to a lower dose (1 mg/kg) decreased the need for new doses to achieve adequate sedation (2.9% and 5% *vs.* 16%), with no increase in the risk of adverse effects (14.3% and 10% *vs.* 10%) or the duration of sedation in minutes (24.5 min and 23 min *vs.* 23 min).[83]

Ketamine can cause transient laryngospasm, as well as apnea, hypersalivation, vomiting, and restlessness in recovery. It inhibits the reuptake of catecholamines, resulting in a sympathomimetic effect, which causes an increase in blood pressure, heart rate, and cardiac output. A prospective study of 11 adult patients with ischemic heart disease showed a reduction in left ventricular systolic and diastolic function.[84] Reduction of systolic pressure secondary to decreased ejection fraction after ketamine use was demonstrated in a small group of patients in the pediatric age group.[85] The catecholaminergic effects mask myocardial depression. Further studies are needed to clarify the hemodynamic effects of this drug.

The post-sedation emergency phenomenon with ketamine, rare in pediatrics, can manifest itself through crying, lucid dreaming, hallucinations, and, more rarely, severe delirium. It is more common in adolescents when the drug is administered intramuscularly or at high doses.[86,87] There is no evidence that an infusion of midazolam as premedication to ketamine reduces the incidence of emergency phenomena. Wathen et al. found similar rates of emergence phenomena in pediatric patients receiving ketamine alone (7.1%) and in those receiving it in association with midazolam (6.2%).[88] Also, another study published by Sherwin et al. did not demonstrate any additional benefit of midazolam to prevent emergency phenomena.[89]

Ketamine is contraindicated in patients younger than 3 months due to the risk of airway complications, and in schizophrenic patients, due to the risk of psychotic stimulation.[90] Risk factors for adverse airway and breathing events are high intravenous doses, age less than 2 years or greater than 13 years, and co-administration of anticholinergics and benzodiazepines.[91] The associated use of atropine may reduce hypersalivation, but does not reduce the frequency of adverse events.[92] Two randomized studies have demonstrated the reduction of hypersalivation with the prophylactic use of atropine, with no positive impact on the rate of adverse events.[93,94]

The use of ketamine should be avoided in patients with heart disease, with active pulmonary pathologies, or with central nervous system abnormalities. Currently, there is no contraindication to its use in traumatic brain injury, as there is no increase in the risk of intracranial hypertension or neurological complications, even in severe cases.[95–98] A systematic review showed no significant difference in cerebral perfusion pressure, neurological outcome, length of stay in the intensive care unit (ICU), or mortality when the use of ketamine was compared with other sedatives.[99] However, the relative contra-indication still remains in patients with intracranial masses, intracranial anatomical alterations, and hydrocephalus.[100]

Propofol

Propofol is a hypnotic sedative agent with fast and short-acting anesthetic properties, corresponding to 2,6-diisopropylphenol, which exerts its hypnotic action through the activation of GABA, a central inhibitory neurotransmitter.[101,102] It can be used in brief procedures, associated or unassociated with analgesic agents, such as fentanyl and ketamine.[103,104]

For longer procedures, such as in MRI sedation, propofol can be used under continuous infusion.[105] Sebe et al. published a prospective pediatric study with a cohort of 200 pediatric patients undergoing imaging examinations, in which propofol was more effective than midazolam in terms of sedation effectiveness and shorter recovery time, with no statistical difference in the rate of adverse events between the drugs.[106] Studies comparing propofol, pentobarbital, and dexmedetomidine in MRI sedation were also favorable to the first drug.[107–109] More complex and time-consuming imaging studies can be performed effectively with continuous infusion, without increasing recovery time or risk of adverse effects.[110]

The metabolism of propofol is hepatic, the elimination is biphasic (with the initial phase at 40 min and terminal phase at 4–7 h), and excretion is mostly urinary (88%). Administration is exclusively IV, usually associated with pain during infusion, an effect that can be reduced with pre-treatment of the vein with lidocaine, *i.e.*, previous administration of

small doses of opioid or ketamine or infusion into large-caliber veins.[111]

Propofol has several cardiovascular effects, with hypotension being the most significant.[112] This is due to arterial vasodilation through the reduction of sympathetic tonus, but also because it affects myocardial contractility and cardiac output.[113] These effects may be exacerbated in hypovolemic patients, or patients with pre-existing heart disease or the concomitant use of other cardiac depressant drugs. Bolus administration of saline 0.9% at 20 mL/kg prior to propofol infusion did not reduce the risk of hypotension in pediatric patients when compared to the control group in a randomized study published by Jager et al.[114] The decrease in the systemic vascular resistance induced by the drug may be harmful in patients with congenital heart disease; however, the heart rate does not change significantly. Apnea and airway obstruction is frequent, even at usual doses, since propofol depresses the CNS, which can reduce respiratory rate and pulmonary volume.[115] The risk of respiratory depression increases proportionally to the infusion velocity as well as the risk of bradycardia, and hypotension is associated with higher doses.[116,117] It is contraindicated in patients with allergy to eggs, soybeans, and their derivatives.[118]

Despite the adverse effects, propofol is safe and effective when performed with adequate monitoring. Mallory et al., in a retrospective study that analyzed 25,433 episodes of sedation with propofol, showed a severe adverse event rate, such as airway obstruction, apnea, and oxygen saturation drop in 2.2%, with no associated death reports related to this drug.[104] Chiaretti et al. reviewed 36,156 procedures and obtained an even lower complication rate of 0.75%.[119]

Propofol infusion syndrome is defined as refractory acute bradycardia progressing to asystole, metabolic acidosis, rhabdomyolysis, hyperlipidemia, and hepatic steatosis. It is described in severely-ill pediatric patients receiving this medication for a prolonged period of time (>48 h) and at high doses (>4 mcg/kg/min).[120]

Ketofol

The use of ketamine and propofol in association, known as ''ketofol,'' has become popular due to the possibility of counterbalancing the side effects of each medication and enhanced sedation, increasing efficacy and safety.[121] Ketamine maintains the respiratory drive, prevents hypotension and bradycardia, and provides analgesia, while propofol reduces the incidence of nausea and vomiting, in addition to hypothetically prevents emergency reactions.[122]

When compared to propofol as a single drug, the use of ketofol in pediatric patients resulted in fewer respiratory adverse events, hypotension, and bradycardia, as well as fewer additional doses of the drug.[123] A meta-analysis of 932 patients showed fewer respiratory adverse events with the ketofol group compared to propofol (29% *vs.* 35.4%), with no significant difference in the proportion of general adverse events (38.8% *vs.* 42.5%).[124] Another meta-analysis by Jalili et al. demonstrated that ketofol significantly reduced respiratory and cardiovascular complications (hypotension and bradycardia).[125]

There is no consensus regarding which dose of each drug should be used when in combination, with the suggestion of an initial dose of 0.5 mg/kg of propofol and 1 mg/kg of ketamine. No difference in the quality of sedation or safety profile was observed between mixtures at the proportions of 1:1 and 1:4 of ketamine and propofol in adults.[126] Further studies on the use of ketofol in pediatric patients are required to elucidate its advantages and disadvantages as a sedative agent.[127]

Dexmedetomidine

Dexmedetomidine (DEX) is an alpha-2 adrenergic agonist with an action that is not mediated by GABA, which promotes sedation without decreasing the respiratory drive.[128] Despite its off-label use in pediatrics, its use has been increasingly used for short procedures and also for situations requiring prolonged sedation.[129] It can be used as a single agent or in combination with midazolam, ketamine, or opioids.[130,131] In the emergency department, it is mainly used for imaging studies.[132,133] Due to its unique pharmacological characteristics, DEX is used to induce an electroencephalogram (EEG) pattern similar to that of natural sleep.[134,135] It is an effective alternative to midazolam in sedation during upper digestive endoscopy, with better sedation potential and fewer adverse effects.[136]

It has hepatic metabolism and urinary excretion (95%), with IV, IN, oral, and oral gastric mucosa routes, with the latter showing less bioavailability.[128] It can cause hypotension, bradycardia, and sinus arrhythmia.[130,137] Due to its pharmacological characteristics and its clinical applications, dexmedetomidine appears to be a good alternative to the use of chloral hydrate in pediatric emergency departments after the latter's recent discontinuation of use in Brazil.

Although it has not been approved by the Food and Drug Administration for pediatric use due to lack of data demonstrating its safety profile, studies have already shown that it is a safe sedative, especially in the context of adult and pediatric ICUs.[138] Constantin et al. published a meta-analysis of 1994 adult ICU patients, showing a reduction in hospitalization time, mechanical ventilation time, and delirium occurrence in 48 h, but an increase in cases of bradycardia and hypotension was observed.[139] Berkenbosch et al., in a prospective pediatric study, demonstrated the efficacy and safety of dexmedetomidine for noninvasive procedures.[140]

Etomidate

Etomidate is an imidazole derivative used as an ultra-fast acting sedative-hypnotic agent that binds to GABA receptors in the central nervous system. Commonly used in rapid intubation sequences in children, it may be used in non-painful short-term procedures, such as skull CT, and in painful procedures associated with an analgesic drug. It has few hemodynamic repercussions, and respiratory effects are rare.[141,142]

It is a highly lipophilic drug, with hepatic metabolism and urinary excretion (75%). It is administered exclusively intravenously, and may be irritating at the infusion site; it is preferable to administer it through larger caliber veins or in combination with lidocaine.[141] It can cause myoclonus (without EEG repercussions), nausea, vomiting, apnea, and hypoventilation.[142,143] Di Liddo et al. compared etomidate

and midazolam in the sedation of pediatric patients submitted to fracture reduction and showed a higher proportion of adequately sedated patients in the etomidate group (92% *vs.* 36%), with a shorter time of induction and recovery.[144]

As etomidate inhibits the 11-beta-hydroxylase enzyme, which participates in the production of adrenal hormones, a single dose can suppress the stress-induced cortisol production response and may last 6–8 h.[145,146] Thus, the use of this drug in septic or critically-ill patients, even in a single dose, remains controversial.[145] Nonetheless, its use in healthy patients appears to be well tolerated.[147] Two prospective randomized studies in adults did not demonstrate increased morbidity and mortality or hospital length of stay when etomidate was administered by bolus in the rapid intubation sequence.[148]

Conclusion

Painful diagnostic and therapeutic procedures that frequently require patient collaboration are common in the practice of pediatric emergency. Indication of analgesia and sedation for such procedures should occur after a careful patient assessment, considering the purpose, risks, and benefits associated with the procedure and the use of medications. The use of protocols for this purpose should guide the professional in the choice of medication, the appropriate material, and evaluation of the discharge criteria, thus ensuring quality in care. Analgesia and sedation for procedures requires training of health teams, aiming at safety and effectiveness. Studies have shown the best pharmacological choices for certain procedures, considering the age and health status of each patient, making sedoanalgesia an increasingly common and safer practice in the pediatric emergency room.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Krauss B, Green SM. Procedural sedation and analgesia in children. Lancet. 2006;367:766–80.
2. McCoy S, Lyttle MD, Hartshorn S, Larkin P, Brenner M, O'Sullivan R, et al. A qualitative study of the barriers to procedural sedation practices in paediatric emergency medicine in the UK and Ireland. Emerg Med J. 2016;33:527–32.
3. Mason KP. Challenges in paediatric procedural sedation: political, economic, and clinical aspects. Br J Anaesth. 2014;113. Sii48–62.
4. Gozal D, Mason KP. Pediatric sedation: a global challenge. Int J Pediatr. 2010:701257.
5. Bartolome SM, Cid JL, Freddi N. Analgesia and sedation in children: practical approach for the most frequent situations. J Pediatr (Rio J). 2007;83:S71–82.
6. Miyake RS, Reis AG, Grisi S. Sedation and analgesia for children. Rev Assoc Med Bras. 1998;44:56–64.
7. Carvalho WB, Troster EJ. Sedation and analgesia at the emergency room. J Pediatr (Rio J). 1999;75:S294–306.
8. Manyande A, Cyna AM, Yip P, Chooi C, Middleton P. Non-pharmacological interventions for assisting the induction of anaesthesia in children. Cochrane Database Syst Rev. 2015;14:CD006447.
9. Birnie KA, Noel M, Parker JA, Chambers CT, Uman LS, Kisely SR, et al. Systematic review and meta-analysis of distraction and hypnosis for needle-related pain and distress in children and adolescents. J Pediatr Psychol. 2014;39:783–808.
10. White PF, Way WL, Trevor AJ. Ketamine – its pharmacology and therapeutic uses. Anesthesiology. 1982;56:119–36.
11. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology. 2002;96:1004–17.
12. Büttner W, Finke W. Analysis of behavioural and physiological parameters for the assessment of postoperative analgesic demand in newborns, infants and young children: a comprehensive report on seven consecutive studies. Paediatr Anaesth. 2000;10:303–18.
13. Gonsalves S, Mercer J. Physiological correlates of painful stimulation in preterm infants. Clin J Pain. 1993;9:88–93.
14. Crellin D, Sullivan TP, Babl FE, O'Sullivan R, Hutchinson A. Analysis of the validation of existing behavioral pain and distress scales for use in the procedural setting. Paediatr Anaesth. 2007;17:720–33.
15. Lawrence J, Alcock D, McGrath P, Kay J, MacMurray SB, Dulberg C. The development of a tool to assess neonatal pain. Neonatal Netw. 1993;12:59–66.
16. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: a behavioral scale for scoring postoperative pain in young children. Pediatr Nurs. 1997;23:293–7.
17. Manworren RC, Hynan LS. Clinical validation of FLACC: preverbal patient pain scale. Pediatr Nurs. 2003;29:140–6.
18. Beyer JE, Aradine CR. Content validity of an instrument to measure young children's perceptions of the intensity of their pain. J Pediatr Nurs. 1986;1:386–95.
19. Bieri D, Reeve RA, Champion GD, Addicoat L, Ziegler JB. The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: development, initial validation, and preliminary investigation for ratio scale properties. Pain. 1990;41:139–50.
20. Garra G, Singer AJ, Taira BR, Chohan J, Cardoz H, Chisena E, et al. Validation of the Wong-Baker FACES Pain Rating Scale in pediatric emergency department patients. Acad Emerg Med. 2010;17:50–4.
21. Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. Ann Emerg Med. 1996;27:485–9.
22. Tobias JD, Leder M. Procedural sedation: a review of sedative agents, monitoring, and management of complications. Saudi J Anaesth. 2011;5:395–410.
23. Bellolio MF, Puls HA, Anderson JL, Gilani WI, Murad MH, Barrionuevo P, et al. Incidence of adverse events in paediatric procedural sedation in the emergency department: a systematic review and meta-analysis. BMJ Open. 2016;6:e011384.
24. Cravero JP, Blike GT, Beach M, Gallagher SM, Hertzog JH, Havidich JE, et al. Incidence and nature of adverse events during pediatric sedation/anesthesia for procedures outside the operating room: report from the Pediatric Sedation Research Consortium. Pediatrics. 2006;118:1087–96.
25. Bellolio MF, Gilani WI, Barrionuevo P, Murad MH, Erwin PJ, Anderson JR, 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;23:119–34.
26. American Society of Anesthesiologists Committee. 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 Committee on Standards and Practice Parameters. Anesthesiology. 2011;114:495–511.
27. Godwin SA, Burton JH, Gerardo CJ, Hatten BW, Mace SE, Silvers SM, et al. Clinical policy: procedural sedation and analgesia in the emergency department. Ann Emerg Med. 2014;63, 247–258.e18.
28. Thorpe RJ, Benger J. Pre-procedural fasting in emergency sedation. Emerg Med J. 2010;27:254–61.
29. Hoffman GM, Nowakowski R, Troshynski TJ, Berens RJ, Weisman SJ. Risk reduction in pediatric procedural sedation by application of an American Academy of Pediatrics/American Society of Anesthesiologists process model. Pediatrics. 2002;109:236–43.
30. Clark M, Birisci E, Anderson JE, Anliker CM, Bryant MA, Downs C, et al. The risk of shorter fasting time for pediatric deep sedation. Anesth Essays Res. 2016;10:607–12.
31. Butler MG, Hayes BG, Hathaway MM, Begleiter ML. Specific genetic diseases at risk for sedation/anesthesia complications. Anesth Analg. 2000;91:837–55.
32. Malviya S, Voepel-Lewis T, Tait AR. Adverse events and risk factors associated with the sedation of children by nonanesthesiologists. Anesth Analg. 1997;85:1207–13.
33. Jirativanont T, Manomayangkul K, Udomphorn Y, Yokubol B, Saguansab A, Kraiprasit K, et al. Incidence and risk factors for adverse events during anesthesiologist-led sedation or anesthesia for diagnostic imaging in children: a prospective, observational cohort study. Asi Biomed. 2017;9:649–58.
34. Caperell K, Pitetti R. Is higher ASA class associated with an increased incidence of adverse events during procedural sedation in a pediatric emergency department? Pediatr Emerg Care. 2009;25:661–4.
35. Nargozian C. The airway in patients with craniofacial abnormalities. Paediatr Anaesth. 2004;14:53–9.
36. Heinrich S, Birkholz T, Ihmsen H, Irouschek A, Ackermann A, Schmidt J. Incidence and predictors of difficult laryngoscopy in 11,219 pediatric anesthesia procedures. Paediatr Anaesth. 2012;22:729–36.
37. Heinrich S, Birkholz T, Irouschek A, Ackermann A, Schmidt J. Incidences and predictors of difficult laryngoscopy in adult patients undergoing general anesthesia: a single-center analysis of 102,305 cases. J Anesth. 2013;27:815–21.
38. Coté CJ, 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: update 2016. Pediatrics. 2016;138, pii: e20161212.
39. Waugh JB, Epps CA, Khodneva YA. Capnography enhances surveillance of respiratory events during procedural sedation: a meta-analysis. J Clin Anesth. 2011;23:189–96.
40. Langhan ML, Shabanova V, Li FY, Bernstein SL, Shapiro ED. A randomized controlled trial of capnography during sedation in a pediatric emergency setting. Am J Emerg Med. 2015;33:25–30.
41. Krauss BS, Krauss BA, Green SM. Procedural sedation and analgesia in children. N Engl J Med. 2014;370:e23.
42. Couloures KG, Beach M, Cravero JP, Monroe KK, Hertzog JH. Impact of provider specialty on pediatric procedural sedation complication rates. Pediatrics. 2011;127:e1154–60.
43. Sauter TC, Hautz WE, Hostettler S, Brodmann-Maeder M, Martinolli L, Lehmann B, et al. Interprofessional and interdisciplinary simulation-based training leads to safe sedation procedures in the emergency department. Scand J Trauma Resusc Emerg Med. 2016;24:97.
44. Farnsworth ST, Egan TD, Johnson SE, Westenskow D. Teaching sedation and analgesia with simulation. J Clin Monit Comput. 2000;16:273–85.
45. Fehr JJ, Chao J, Kuan C, Zhong J. The important role of simulation in sedation. Curr Opin Anaesthesiol. 2016;29:S14–20.
46. Krauss B, Green SM. Training and credentialing in procedural sedation and analgesia in children: lessons from the United States model. Paediatr Anaesth. 2008;18:30–5.
47. Zaveri PP, Davis AB, O'Connell KJ, Willner E, Schinasi DA, Ottolini M. Virtual reality for pediatric sedation: a randomized controlled trial using simulation. Cureus. 2016;8:e486.
48. Maghraby N, Pearson E, Xue X, Colacone A, Afilalo M. What is the impact of the implementation of an evidence based procedural sedation protocol in the emergency department? J Clin Trials. 2016;6:283.
49. Blumer JL. Clinical pharmacology of midazolam in infants and children. Clin Pharmacokinet. 1998;35:37–47.
50. Wright SW, Chudnofsky CR, Dronen SC, Kothari R, Birrer P, Blanton DM, et al. Comparison of midazolam and diazepam for conscious sedation in the emergency department. Ann Emerg Med. 1993;22:201–5.
51. Ilkhanipour K, Juels CR, Langdorj MI. Pediatric pain control and conscious sedation: a survey of emergency medicine residencies. Acad Emerg Med. 1994;1:368–72.
52. Sukys GA, Schvartsman C, Reis AG. Evaluation of rapid sequence intubation in the pediatric emergency department. J Pediatr (Rio J). 2011;87:343–9.
53. Notterman DA. Sedation with intravenous midazolam in the pediatric intensive care unit. Clin Pediatr (Phila). 1997;36:449–54.
54. Griffith N, Howell S, Mason DG. Intranasal midazolam for premedication of children undergoing day-case anesthesia: comparison of two delivery systems with assessment of intra-observer variability. Br J Anesth. 1998;81:865–9.
55. Sahyoun C, Kraus B. Clinical implications of pharmacokinetics and pharmacodynamics of procedural sedation agents in children. Curr Opin Pediatr. 2012;24:225–32.
56. Smith D, Cheek H, Denson B, Pruitt CM. Lidocaine pretreatment reduces the discomfort of intranasal midazolam administration: a randomized, double-blind, placebo-controlled trial. Acad Emerg Med. 2017;24:161–7.
57. Chiaretti A, Barone G, Rigante D, Ruggiero A, Pierri F, Barbi E, et al. Intranasal lidocaine and midazolam for procedural sedation in children. Arch Dis Child. 2011;96:160–3.
58. Lucas SS, Nasr VG, Ng AJ, Joe C, Bond M, DiNardo JA. Pediatric Cardiac Intensive Care Society 2014 consensus statement: pharmacotherapies in cardiac critical care: sedation, analgesia and muscle relaxant. Pediatr Crit Care Med. 2016;17: S3–15.
59. Shannon M, Albers G, Burkart K, Liebelt E, Kelley M, McCubbin MM, et al. Safety and efficacy of flumazenil in the reversal of benzodiazepine-induced conscious sedation. J Pediatr. 1997;131:582–6.
60. Inturrisi CE. Clinical pharmacology of opioids for pain. Clin J Pain. 2002;18:S3–13.
61. Stanski DR, Greenblatt DJ, Lowenstein E. Kinetics of intravenous and intramuscular morphine. Clin Pharmacol Ther. 1978;24:52–9.
62. Barcelos A, Garcia PC, Portela JL, Piva JP, Garcia JP, Santana JC. Comparison of two analgesia protocols for the treatment of pediatric orthopedic emergencies. Rev Assoc Med Bras. 2015;61:362–7.
63. Gupta M, Msambichaka L, Ballas SK, Gupta K. Morphine for the treatment of pain in sickle cell disease. Sci World J. 2015;2015:540154.
64. Martin LD, Jimenez N, Lynn AM. A review of perioperative anesthesia and analgesia for infants: updates and trends to watch. F1000Res. 2017;6:120.
65. McRorie TI, Lynn AM, Nespeca MK, Opheim KE, Slattery JT. The maturation of morphine clearance and metabolism. Am J Dis Child. 1992;146:972–6.
66. Lynn A, Nespeca MK, Bratton SL, Strauss SG, Shen DD. Clearance of morphine in postoperative infants during intravenous

infusion: the influence of age and surgery. Anesth Analg. 1998;86:958–63.
67. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. Farmacologia. 7th ed. Rio de Janeiro: Elsevier; 2012.
68. Tobias JD. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. Crit Care Med. 2000;28:2122–32.
69. Feierman DE, Lasker JM. Metabolism of fentanyl, a synthetic opioid analgesic, by human liver microsomes: role of CYP3A4. Drug Metab Dispos. 1996;24:932–9.
70. Labroo RB, Paine MF, Thummel KE, Kharasch ED. Fentanyl metabolism by human hepatic and intestinal cytochrome P4503A4: implications for interindividual variability in disposition, efficacy, and drug interactions. Drug Metab Dispos. 1997;25:1072–80.
71. Singleton MA, Rosen JI, Fisher DM. Plasma concentrations of fentanyl in infants, children and adults. Can J Anaesth. 1987;34:152–5.
72. Lexi-Comp Inc. Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online. Hudson, OH: Lexi-Comp, Inc, April–May 2017; 2017.
73. Miner JR, Kletti C, Herold M, Hubbard D, Biros MH. Randomized clinical trial of nebulized fentanyl citrate *versus* i.v. fentanyl citrate in children presenting to the emergency department with acute pain. Acad Emerg Med. 2007;14:895–8.
74. Borland M, Milsom S, Esson A. Equivalency of two concentrations of fentanyl administered by the intranasal route for acute analgesia in children in a paediatric emergency department: a randomized controlled trial. Emerg Med Aust. 2011;23:202–8.
75. Young PA, Nicol MF, Kendall JM, Harrington AP. A prospective randomized pilot comparison of intranasal fentanyl and intramuscular morphine for analgesia in children presenting to the emergency department with clinical fractures. Emerg Med. 1999;11:90–4.
76. Roback MG, Wathen JE, Bajaj L, Bothner JP. Adverse events associated with procedural sedation and analgesia in a pediatric emergency department: a comparison of common parenteral drugs. Acad Emerg Med. 2005;12:508–13.
77. Fleischman RJ, Frazer DG, Daya MJ, Jui J, Newgard CD. Effectiveness and safety of fentanyl compared with morphine for out-of-hospital analgesia. Prehosp Emerg Care. 2010;14:167–75.
78. Barsan WG, Seger D, Danzl DF, Ling LJ, Bartlett R, Buncher R, et al. Duration of antagonistic effects of nalmefene and naloxone in opiate-induced sedation for emergency department procedures. Am J Emerg. 1989;7:155–61.
79. Barrons RW, Woods JA. Low-dose naloxone for prophylaxis of postoperative nausea and vomiting: a systematic review and meta-analysis. Pharmacotherapy. 2017;37:546–54.
80. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med. 2011;57:449–61.
81. Deasy C, Babl FE. Intravenous *vs* intramuscular ketamine for pediatric procedural sedation by emergency medicine specialists: a review. Paediatr Anaesth. 2010;20:787–96.
82. Green SM, Roback MG, Krauss B, Brown L, McGlone RG, Agrawal D, et al. Emergency Department Ketamine Meta-Analysis Study Group. Predictors of emesis and recovery agitation with emergency department ketamine sedation: an individual-patient data meta-analysis of 8,282 children. Ann Emerg Med. 2009;54:171–80.
83. Kannikeswaran N, Lieh-Lai M, Malian M, Wang B, Farooqi A, Roback MG. Optimal dosing of intravenous ketamine for procedural sedation in children in the ED – a randomized controlled trial. Am J Emerg Med. 2016;34:1347–53.
84. Jakobsen CJ, Torp P, Vester AE. Ketamine reduce left ventricular systolic and diastolic function in patients with ischaemic heart disease. Acta Anaesthesiol Scand. 2010;54:1137–44.
85. Eken C, Serinken M, Dogan M. Ketamine may be related to reduced ejection fraction in children during the procedural sedation. Hum Exp Toxicol. 2016;36:106–10.
86. Treston G, Bell A, Cardwell R, Fincher G, Chand D, Cashion G. What is the nature of the emergence phenomenon when using intravenous or intramuscular ketamine for paediatric procedural sedation? Emerg Med Australas. 2009;21:315–22.
87. Green SM, Roback MG, Krauss B, Brown L, McGlone RG, Agrawal D, et al. Predictors of emesis and recovery agitation with emergency department ketamine sedation: an individual-patient data meta-analysis of 8,282 children. Ann Emerg Med. 2009;54:171–80.
88. Wathen JE, Roback MG, Mackenzie T, Bothner JP. Does midazolam alter the clinical effects of intravenous ketamine sedation in children? A double-blind, randomized, controlled, emergency department trial. Ann Emerg Med. 2000;36:579–88.
89. Sherwin TS, Green SM, Khan A, Chapman DS, Dannenberg B. Does adjunctive midazolam reduce recovery agitation after ketamine sedation for pediatric procedures? A randomized, double-blind, placebo-controlled trial. Ann Emerg Med. 2000;35:229–38.
90. Lahti AC, Koffel B, LaPorte D, Tamminga CA. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology. 1995;13:9–19.
91. Green SM, Roback MG, Krauss B, Brown L, McGlone RG, Agrawal D, et al. Predictors of airway and respiratory adverse events with ketamine sedation in the emergency department: an individual-patient data meta-analysis of 8,282 children. Ann Emerg Med. 2009;54:158–68.
92. Heinz P, Geelhoed GC, Wee C, Pascoe EM. Is atropine needed with ketamine sedation? A prospective, randomised, double blind study. Emerg Med J. 2006;23:206–9.
93. Kye YC, Rhee JE, Kim K, Kim T, Jo YH, Jeong JH, et al. Clinical effects of adjunctive atropine during ketamine sedation in pediatric emergency patients. Am J Emerg Med. 2012;30:1981–5.
94. Asadi P, Ghafouri HB, Yasinzadeh M, Kasnavieh SM, Modirian E. Ketamine and atropine for pediatric sedation: a prospective double-blind randomized controlled trial. Pediatr Emerg Care. 2013;29:136–9.
95. Bar-Joseph G, Guilburd Y, Tamir A, Guilburd JN. Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. J Neurosurg Pediatr. 2009;4:40–6.
96. Zeiler FA, Teitelbaum J, West M, Gillman LM. The ketamine effect on ICP in traumatic brain injury. Neurocrit Care. 2014;21:163–73.
97. Wang X, Ding X, Tong Y, Zong J, Zhao X, Ren H, et al. Ketamine does not increase intracranial pressure compared with opioids: meta-analysis of randomized controlled trials. J Anesth. 2014;28:821–7.
98. Zeiler FA, Teitelbaum J, West M, Gillman LM. The ketamine effect on intracranial pressure in nontraumatic neurological illness. J Crit Care. 2014;29:1096–106.
99. Cohen L, Athaide V, Wickham ME, Doyle-Waters MM, Rose NG, Hohl CM. The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: a systematic review. Ann Emerg Med. 2015;65:43–51.
100. Green SM, Andolfatto G, Krauss BS. Ketamine and intracranial pressure: no contraindication except hydrocephalus. Ann Emerg Med. 2015;65:52–4.
101. Morgan DJ, Campbell GA, Crankshaw DP. Pharmacokinetics of propofol when given by intravenous infusion. Br J Clin Pharmacol. 1990;30:144–8.
102. Marik PE. Propofol: therapeutic indications and side-effects. Curr Pharm Des. 2004;10:3639–49.
103. Godambe SA, Elliot V, Matheny D, Pershad J. Comparison of propofol/fentanyl *versus* ketamine/midazolam for brief

orthopedic procedural sedation in a pediatric emergency department. Pediatrics. 2003;112:116–23.
104. Mallory MD, Baxter AL, Yanosky DJ, Cravero JP. Pediatric Sedation Research Consortium. Emergency physician-administered propofol sedation: a report on 25,433 sedations from the pediatric sedation research consortium. Ann Emerg Med. 2011;57:462–8.
105. Srinivasan M, Turmelle M, Depalma LM, Mao J, Carlson DW. Procedural sedation for diagnostic imaging in children by pediatric hospitalists using propofol: analysis of the nature, frequency, and predictors of adverse events and interventions. J Pediatr. 2012;160:801–6.
106. Sebe A, Yilmaz HL, Koseoglu Z, Ay MO, Gulen M. Comparison of midazolam and propofol for sedation in pediatric diagnostic imaging studies. Postgrad Med. 2014;126:225–30.
107. Mallory MD, Baxter AL, Kost SI. Pediatric Sedation Research Consortium. Propofol vs pentobarbital for sedation of children undergoing magnetic resonance imaging: results from the Pediatric Sedation Research Consortium. Paediatr Anaesth. 2009;19:601–11.
108. Pershad J, Wan J, Anghelescu DL. Comparison of propofol with pentobarbital/midazolam/fentanyl sedation for magnetic resonance imaging of the brain in children. Pediatrics. 2007;120:e629–36.
109. Fang H, Yang L, Wang X, Zhu H. Clinical efficacy of dexmedetomidine *versus* propofol in children undergoing magnetic resonance imaging: a meta-analysis. Int J Clin Exp Med. 2015;8:11881–9.
110. Griffiths MA, Kamat PP, McCracken CE, Simon HK. Is procedural sedation with propofol acceptable for complex imaging? A comparison of short *vs*. prolonged sedations in children. Pediatr Radiol. 2013;43:1273–8.
111. Jalota L, Kalira V, George E, Shi YY, Hornuss C, Radke O, et al. Prevention of pain on injection of propofol: systematic review and meta-analysis. BMJ. 2011;342:d1110.
112. Chidambaran V, Costandi A, D'Mello A. Propofol: a review of its role in pediatric anesthesia and sedation. CNS Drugs. 2015;29:543–63.
113. Robinson BJ, Ebert TJ, O'Brien TJ, Colinco MD, Muzi M. Mechanisms whereby propofol mediates peripheral vasodilation in humans. Sympathoinhibition or direct vascular relaxation? Anesthesiology. 1997;86:64–72.
114. Jager MD, Aldag JC, Deshpande GG. A presedation fluid bolus does not decrease the incidence of propofol-induced hypotension in pediatric patients. Hosp Pediatr. 2015;5:85–91.
115. Marik PE. Propofol: therapeutic indications and side effects. Curr Pharm Des. 2004;10:3639–49.
116. Dosani M, McCormack J, Reimer E, Brant R, Dumont G, Lim J, et al. Slower administration of propofol preserves adequate respiration in children. Paediatr Anaesth. 2010;20:1001–8.
117. Milius EM, Papademetrious TR, Heitlinger LA. Retrospective review of propofol dosing for procedural sedation in pediatric patients. J Pediatr Pharmacol Ther. 2012;17:246–51.
118. Murphy A, Campbell DE, Baines D, Mehr S. Allergic reactions to propofol in egg-allergic children. Anesth Analg. 2011;113:140–4.
119. Chiaretti A, Benini F, Pierri F, Vecchiato K, Ronfani L, Agosto C, et al. Safety and efficacy of propofol administered by paediatricians during procedural sedation in children. Acta Paediatr. 2014;103:182–7.
120. Vasile B, Rasulo F, Candiani A, Latronico N. The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. Intensive Care Med. 2003;29:1417–25.
121. Alletag MJ, Auerbach MA, Baum CR. Ketamine, propofol, and ketofol use for pediatric sedation. Pediatr Emerg Care. 2012;28, 1391-5; quiz 1396-8.
122. Andolfatto G, Willman E. A prospective case series of pediatric procedural sedation and analgesia in the emergency department using single-syringe ketamine-propofol combination (ketofol). Acad Emerg Med. 2010;17:194–201.
123. David H, Shipp J. A randomized controlled trial of ketamine/propofol *versus* propofol alone for emergency department procedural sedation. Ann Emerg Med. 2011;57:435–41.
124. Yan JW, McLeod SL, Iansavitchene A. Ketamine-propofol *versus* propofol alone for procedural sedation in the emergency department: a systematic review and meta-analysis. Acad Emerg Med. 2015;22:1003–13.
125. Jalili M, Bahreini M, Doosti-Irani A, Masoomi R, Arbab M, Mirfazaelian H. Ketamine-propofol combination (ketofol) *vs* propofol for procedural sedation and analgesia: systematic review and meta-analysis. Am J Emerg Med. 2016;34:558–69.
126. Miner JR, Moore JC, Austad EJ, Plummer D, Hubbard L, Gray RO. Randomized, double-blinded, clinical trial of propofol, 1:1 propofol/ketamine, and 4:1 propofol/ketamine for deep procedural sedation in the emergency department. Ann Emerg Med. 2015;65:479–88.
127. Green SM, Andolfatto G, Krauss BS. Ketofol for procedural sedation revisited: pro and con. Ann Emerg Med. 2015;65:489–91.
128. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. Anesthesiology. 1992;77:1125–33.
129. Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. Pediatr Crit Care Med. 2007;8:115–31.
130. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. Br J Anaesth. 2015:115171–82.
131. Mason KP, Lerman J. Review article: dexmedetomidine in children: current knowledge and future applications. Anesth Analg. 2011;113:1129–42.
132. Mason KP, Lubisch NB, Robinson F, Roskos R. Intramuscular dexmedetomidine sedation for pediatric MRI and CT. AJR Am J Roentgenol. 2011;197:720–5.
133. Mekitarian Filho E, Robinson F, de Carvalho WB, Gilio AE, Mason KP. Intranasal dexmedetomidine for sedation for pediatric computed tomography imaging. J Pediatr. 2015;166:1313–5.
134. Mason KP, O'Mahony E, Zurakowski D, Libenson MH. Effects of dexmedetomidine sedation on the EEG in children. Paediatr Anaesth. 2009;19:1175–83.
135. Baier NM, Mendez SS, Kimm D, Velazquez AE, Schroeder AR. Intranasal dexmedetomidine: an effective sedative agent for electroencephalogram and auditory brain response testing. Paediatr Anaesth. 2016;26:280–5.
136. Zhang F, Sun HR, Zheng ZB, Liao R, Liu J. Dexmedetomidine versus midazolam for sedation during endoscopy: a meta-analysis. Exp Ther Med. 2016;11:2519–24.
137. Carney L, Kendrick J, Carr R. Safety and effectiveness of dexmedetomidine in the pediatric intensive care unit (SAD-PICU). Can J Hosp Pharm. 2013;66:21–7.
138. Department of Health and Human Services. Public Health Service. Food and Drug Administration. Center for Drug Evaluation and Research. Office of Surveillance and Epidemiology. Pediatric postmarketing pharmacovigilance and drug utilization review. Precedex (dexmedetomidine HCl injection); 2016 Mar. Available from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM494470.pdf [cited 18.11.16].
139. Constantin JM, Momon A, Mantz J, Payen JF, De Jonghe B, Perbet S, et al. Efficacy and safety of sedation with dexmedetomidine in critical care patients: a meta-analysis of randomized controlled trials. Anaesth Crit Care Pain Med. 2016;35:7–15.

140. Berkenbosch JW, Wankum PC, Tobias JD. Prospective evaluation of dexmedetomidine for noninvasive procedural sedation in children. Pediatr Crit Care Med. 2005;6:435–9, quiz 440.
141. Forman SA. Clinical and molecular pharmacology of etomidate. Anesthesiology. 2011;114:695–707.
142. Falk J, Zed PJ. Etomidate for procedural sedation in the emergency department. Ann Pharmacother. 2004;38:1272–7.
143. Mandt MJ, Roback MG, Bajaj L, Galinkin JL, Gao D, Wathen JE. Etomidate for short pediatric procedures in the emergency department. Pediatr Emerg Care. 2012;28:898–904.
144. Di Liddo L, D'Angelo A, Nguyen B, Bailey B, Amre D, Stanciu C. Etomidate *versus* midazolam for procedural sedation in pediatric outpatients: a randomized controlled trial. Ann Emerg Med. 2006;48:433–40, 440.e1.
145. Majesko A, Darby JM. Etomidate and adrenal insufficiency: the controversy continues. Crit Care. 2010;14:338.
146. Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med. 1984;310:1415–21.
147. Jones AE. The etomidate debate. Ann Emerg Med. 2010;56:490–1.
148. Tekwani KL, Watts HF, Sweis RT, Rzechula KH, Kulstad EB. A comparison of the effects of etomidate and midazolam on hospital length of stay in patients with suspected sepsis: a prospective, randomized study. Ann Emerg Med. 2010;56:481–9.