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Pain treatment of infants and children in emergency

Giuseppe A. Marraro

ABSTRACT

***Objective*:** To review pain therapies utilized in pediatric age in intra and extra hospital emergency, according to present updated evidence and best practice. ***Research and data*:** Literature search using the key words pain, analgesia, sedation, infant, children, pediatric, emergency, postoperative care, PICU, NICU, mechanical ventilation, alone or associated. ***Intervention*:** None. ***Results*:** A progression in the handling according to the needs of children is necessary in order to apply the appropriate pain treatment reducing side effects in emergency and immediately post-care. Even in less stressed environments, the best way to assess children's pain remains controversial, with many different methods available. Prolonged analgesia must be titrated during the assessing phase (1-3 hours), the reassessing process for confirming analgesic efficacy and finally the re-evaluation of analgesia in order to highlight the efficacy and adverse effects. ***Conclusions*:** Assessment of pain in children is one of the most challenging problems in emergency settings, where the interplay of emotion, fear and pain are so difficult to separate, and the time available for assessment is limited. No consensus exists on which pharmacologic regimens for procedural sedation/analgesia are safest and most effective in emergency, and in several cases the children still are undertreated.

PREFACE

In this review is considered the pain therapies utilized in pediatric age in emergency, including intra and extra-hospital management. The aim of the study was to present updated evidences and best practices leaving the identification of better treatment for the specific infant and child to the single physician in the peculiar context of emergency. I apologize to those whose favorite pain treatment has been left out. Publications by 1990 and by 2010 have been consulted and these provided useful suggestion for inclusion in this review.

A literature search using the key words pain, analgesia, sedation, infant, children, emergency, postoperative care, PICU, NICU, mechanical ventilation, alone or associated was used. Searches were undertaken of MEDLINE, SCOPUS, OVID, PsycLIT, EMBASE, CINAHL, PsyINFO, and CONSORT. RCTs were sought in references of all identified studies, meta-analyses and reviews.

INTRODUCTION

In the last 20 years there have been dramatic changes in managing neonatal and pediatric pain. The use of innovative techniques for the

Author's affiliation: Ass. Prof. Anesthesia and Intensive Care, University of Milan, Italy. F. Director of Anesthesia and Intensive Care Dept. Pediatric Intensive Care Unit. Fatebenefratelli and Ophthalmiatric General Hospital, University Affiliated, Milan, Italy.

Reprint's request: Dr. G.A. Marraro, MD, Ass. Prof. University Milan, Italy. E-mail: gmarraro@picu.it.

management of pain (e.g. loco-regional anesthesia, continuous infusion of opioids), the awareness of severe complications connected with insufficient pain relief and the neuro-hormonal sequels connected with pain, and the possibility to control and treat respiratory depression and apnea in suitable environments (e.g. intensive care unit or recovery room) created a new perspective due to which at present there is no reason why neonates, infants and children should be denied adequate analgesia [1, 2].

There is clear evidence that emergency departments are poor at children's acute pain management and this appears to be true across all ages [3]. Disparity exists between perceived and documented emergency department pain management practices for children. Quality improvement initiatives should focus on improving pain assessment in infants, treating moderate to severe pain in children of all age groups, and education of health care providers in pain management strategies. In one study was demonstrated that fifty percent of patients in moderate to severe pain would be offered an analgesic. Six- to 15-year-old children would be offered opioids more often than children aged 0 to 1 and 2 to 5 years. Offering higher potency narcotic analgesics was associated with patient's age, geographic location of the facility, and emergency department volume [4].

Analgesia of children for painful procedures can be carried out intra and extra hospital environment. More frequently is applied in emergency department, in intensive care and in surgical theatre where the child may be undergoing suturing or fracture reduction, burns dressing or changing and treatment for joint dislocations. No consensus exists on which pharmacologic regimens for procedural sedation/analgesia are safest and most effective in emergency [5] and in several cases the children are undertreated. Cimpello et al. demonstrated that most children with an extremity fracture and greater than one-third of children with a severe fracture did not receive pain medications in the emergency department [6] confirming that in several cases the children still are undertreated.

Methods for evaluating the intensity of pain in emergency

Assessment of pain in children is one of the most challenging problems in emergency settings, where the interplay of emotion, fear and pain are so difficult to separate, and the time available for assessment is limited. Even in less stressed environments, the best way to assess children's pain remains controversial, with many different methods available. Use of pain assessment scales for infants is limited and one of the fundamental difficulties encountered in children is the cognitive and language skills that are still evolving and in several emergency conditions, the child is comatose and/or not collaborative [7, 8].

Several methods for evaluating the intensity of pain and efficacy of applied therapy have been proposed for conscious and not conscious patient, collaborative or not collaborative children in emergency. General assessment tools for evaluating the intensity of pain in infants and children must take in account:

- Facial expression, body position and physical movement, cry, arterial blood pressure, heart rate, skin color, oxygen saturation, and respiratory rate;

- Sleeplessness, alertness, calmness, and agitation.

However, several of these signs and symptoms could be affected by non-painful conditions and in some case could be difficult to differentiate the real origin of the clinical sign and consequently to evaluate the presence and the intensity of pain [9].

There are many different and specific pain assessment tools for conscious and collaborative children in emergency [10]. Observational (behavioral) Scales of pain [11, 12] and CHEOPS (Children's Hospital of Eastern Ontario Pain Scale) are useful for children aged 3 to 18 years [13] and The FLACC (Face, Legs, Activity, Cry, Consolability) has been shown to provide a simple framework to assess pain in children 2 months to 7 years of age [14]. The most comprehensively validated is the Oucher scale [15]. This tool consists of two scales: one photographic and the other numerical,

arranged vertically beside each other. Younger children are stimulated to self report pain using the photographic scale, while older children, from age seven upwards, are encouraged to use the numerical scale.

"Evendol" is a newer behavioural scale used to objectively assess the pain felt by children under 7 in pediatric emergency departments. Boasting excellent validity criteria and easy to use, it also differentiates pain and anxiety when caring for children in pain [16].

The Manchester is another useful pain scale, cannot be used interchangeably with the Oucher pain scales [17] although they measure the same phenomenon – pain – in a similar fashion, and so do have convergent validity.

The COVERS scale is a valid pain scale that can be used in the clinical setting to assess pain in newborns and infants. Concurrent validity was established by comparing the COVERS scale to previously validated pain scales, namely the PIPP [18] and NIPS [19], and demonstrating a high degree of correlation.

In infants and toddlers, the Objective Pain Scale (OPS) is easy to use [20] and the Toddler-Preschooler Postoperative Pain Scale (TPPPS) [21] has been found to track pain intensity and pain control also in emergency. These are the most commonly used scales in this range of age.

Children who have difficulty communicating their pain (e.g. children, hearing and cognitively impaired patients) require special attention. The needs of children whose educational or cultural background differs significantly from that of their health care team should be taken into account, with scales modified to suit the individual needs of patients. Patients who do not speak the country language should be given the opportunity to communicate in their chosen language through an interpreter.

Whilst children in general are reported to receive less effective pain management than adults, handicapped children may be at particular risk of having their pain underestimated and undertreated [22]. Recently, a new assessment tools, the Non-communicating Children's Pain Checklist (NCCPC) [23] and Individualized Numeric Rating Scale (INRS) [24] were shown to be a reliable measures for determining pain in these children. NCCPC later has been modified for post-operative pain evaluation [25]. The revised FLACC also is able to improve reliability and validity for pain assessment in children with cognitive impairment [26].

Sedation and analgesia

The age of the child needs to be considered when planning sedation and pain relief [27]. Premature or very young infants and all children who may have problems with central respiratory drive (e.g. intoxication, poisoning, brain trauma, and coma) may best benefit from a technique that avoids opioids and central respiratory depressants [28].

Sedation and analgesia provide two general benefits

1. Allow patients to tolerate unpleasant procedures by relieving anxiety, discomfort, or pain;

2. May expedite the conduct of uncomfortable procedures that require that the infant and the child do not move.

Good clinical practice suggests that a combination of non-pharmacological and pharmacological methods should be considered to ensure optimal management of the emotional and physical consequences of diagnostic (e.g. RMI, CT scan, lumbar puncture) and therapeutic procedures (e.g. fracture immobilization) in infants and children. While it may be possible to manage many children undergoing a particular procedure with non-pharmacological techniques, others undergoing the same procedure may require general anesthesia. Distraction, guided imagery, or play therapy can be efficient for many children, particularly those of school age, when procedures are not painful and parental involvement is possible. Anxiety may be best alleviated by good communication, a sympathetic approach and pediatric expertise[29-32].

Pain should be prevented whenever possible by the pre-emptive use of local and systemic analgesics or alternative measures to reduce pain perception[33, 34].

Particular attention must be reserved to infants and children, sedating in emergency, who have any of the following conditions

- Infants aged <1 year and or ex-premature (they are particularly susceptible to the respiratory depressant effects of sedative agents);

- Cardiovascular instability or impaired cardiac function;

- Severe acute and chronic respiratory diseases;

- Impaired bulbar reflexes (may affect ventilation and expose to apnea)

- Hepatic failure (reduced metabolism of sedative drugs results in prolonged duration of action);

- Renal failure (reduced clearance of sedative drugs and active metabolites leading to prolonged duration, late re-sedation and sedation drift);

- Receiving anticonvulsant, opioid and other sedatives therapy (sedative and analgesic drugs may act synergistically with anticonvulsants producing deep sedation; otherwise, some children are resistant to conventional doses of sedative drugs due to hepatic enzyme induction);

- Receiving drugs that can potentiate or have summative action of sedatives (e.g. macrolide antibiotics).

The main factors determining the choice of sedation technique in acute phase and in emergency are[35]

- The environment and clinical setting in which sedation is performed and the availability of skilled personnel to perform and monitor the procedure;

- The child's characteristics (e.g. age, weight, clinical status);

- The risk of procedure and benefit ratio of the applied treatment.

The most common complication of pediatric sedation is respiratory depression and includes upper airway obstruction, hypoventilation (creating hypoxemia and hypercarbia) and apnea resulting in anoxia and cardiac arrest. Individualized dosing of sedative, based on age, weight, co-morbidity, procedure and presence of other drugs, must be used for each child. If a child becomes disinhibited by sedative agents and becomes restless, uncooperative or unmanageable, elective or urgent procedures should be abandoned and re-scheduling for general anesthesia must be considered.

Drugs with sedative properties usually do not produce analgesia and should not be used alone for painful procedures. For prolonged or extensive painful procedures, particularly in younger and /or sicker children, general anesthesia can be considered incorporating multimodal analgesia (i.e. combinations of local anesthesia, opioids, no steroid anti-inflammatory drugs, etc.). Some children may require general anesthesia even for brief procedures, whether painful or painless, because of their level of distress or lack of collaboration.

For painful procedures, appropriate analgesia must be given first to prevent pain before considering sedation. Opioids or combinations of opioids and other sedatives should not be used to sedate children for painless procedures. Associated sedatives and opioids are at a high incidence of side effects and often depress consciousness beyond sedation.

Sedative

Sedation can be obtained with the use of benzodiazepine, nonsteroidal anti-iflammatory drugs ($NSAID_S$) and other analgesic drugs that can have also sedative effects (Table 1).

Benzodiazepines provide sedation and anxiolysis but do not provide analgesia. The side effects and especially the long time taken for elimination connected with the use of diazepam and lorazepam are for the most part resolved with the most commonly used midazolam[36]. Questions remaining unsolved are the problem of respiratory

Table 1: Medication for sedation

	Dose	Advantage	Disadvantages	Side effects
Diazepam (Valium) (benzodiazepine)	IV: 0.1-0.2 mg kg^{-1} Max dose: < 12 y =5mg; >12y=10 mg Oral: 0.25-5 mg kg^{-1} (1-12 yrs old) Rectal: 5-10 mg kg^{-1}	Sedation Anxious status treatment Control of seizures and moderate mio-resolution	Long time elimination and late offset Not analgesic properties. Sleepiness, ataxia, dysartria, irritability, daze. Dependence	Respiratory depression and hypotension Not indication in neuromuscular diseases. Withdrawal syndrome in prolonged use. Porphyry
Lorazepam (benzodiazepine)	IV, IM: 0.05 mg kg^{-1} Oral: 0.05 -0.1 mg kg^{-1} (1-12 yrs old); 1-4 mg kg^{-1} (12-18 yrs old)	Control of seizures and moderate mio-resolution	Long time elimination and late offset. Not analgesic properties Decreased clearance in neonates Sleepiness, ataxia Dependence	Respiratory depression and hypotension. Not indication in neuromuscular diseases. Withdrawal syndrome in prolonged use.
Midazolam (benzodiazepine)	IV bolus or IM 0.05-0.1 mg kg^{-1} IV infusion 0.2-0.4 mg $kg^{-1}h$ Oral: 0.5 mg kg^{-1} Max dose 15 mg	Rapid onset and offset. Minimal cardiorespiratory side effects Can be used by IM, oral, sublingual, nasal or rectal routes	Not analgesic properties	Ataxia, occasional paradoxical agitation.
Flumazenil (benzodiazepine antagonist)	IV 0.05- 0.15 mg kg^{-1} IV infusion: 0.002-0.01 mg kg^{-1} h	Reverse benzodiazepine **Not be used** in mixed intoxication from tricycle anti-depressive and benzodiazepines for risk of seizures and cardiac arrest	Limited experience in pediatric age Benzodiazepines withdrawal syndrome	Seizures in at risk patient Arrhythmias in patients treated with cardiotonic
Chloral hydrate (sedative hypnotic)	Oral/rectal: 25-50 mg kg^{-1} (newborn-12 yrs) Oral/rectal continuous sedation: 20-30 mg kg^{-1}	Non reversible; do not use if a child's neurologic status needs to be followed	Not indication in hepatic and renal failure. Erratic mucosal absorption; Paradoxical excitement and confusional status or sleepiness,ataxia, headache Dependance	Predispose to airway obstruction and respiratory failure Porphyry Gastroenteritis and abdominal distension

depression and hypotension with bradycardia in cases of repeated doses and when high plasmatic level is obtained. There is a wide inter-patient variability in response to benzodiazepines, so titration with an upper dose limit is the first safe approach.

Midazolam is useful when retrograde amnesia, sedation and anxyolisis are recommended and lorazepam may provide an effective alternative, with a longer half-life and more predictable pharmacokinetics without the potential toxicity related to its diluent, propylene glycol, and concern of active metabolites[37-39].

Midazolam can be administered by parenteral (IV, IM), oral, sublingual, nasal or rectal routes. It is rapidly distributed and has an elimination half-life of 70-140 min but this is considerable prolonged in neonates. The onset of action is slower than that seen with intravenous anesthetic agents. Injection over 10-15 s produces smooth induction of sedation whilst minimizing respiratory depression or hypotension.

A new generation drugs with lower side effects are in current use so as the sedative dexmedetomidine.

Dexmedetomidine is an alpha2-agonist for short- term sedation useful in critically ill patients with less opioid requirement compared with propofol. Although dexmedetomidine is labeled only for sedation <24h, it has been administered for longer than 24 h without apparent development of rebound hypertension and tachycardia. Dexmedetomidine appears to be safe and effective agent for sedation in critically hill children even if well-designed studies needed to define its role as a sedative for these patients. In one trial dexmedetomidine infusion did not result in clinically significant respiratory depression, decreased the apnea index, and exhibited some similarity with natural sleep[40].

Analgesics

Nonsteroidal anti-inflammatory drugs (NSDAIs)

Systemic analgesia for control of mild or moderate pain may be acquired with "nonsteroidal anti-inflammatory drugs with (NSDAIs). Acetaminophen (Paracetamol) is a safe and effective analgesic and antipyretic in children including infants and neonates (Table 2). The drug is free of side effects and hepatic toxicity and renal failure are dose-related[41]. Acute intoxication can be treated by acetilcysteine.

Table 2: Recommended dose for acetaminophen administration in neonates, infants and children

Route	Neonate < 1 month	Children 1 month - 12 yrs	Children > 12 yrs
Oral	10-15 mg kg^{-1} (4-6 times/day)	15 mg kg^{-1} (4-6 times/day)	500 mg $^{-1}$ g (4-6 times/day)
Rectal	10-15 mg kg^{-1} (4 times/day)	20 mg kg^{-1} (4-6 times/day)	500 mg $^{-1}$ g (4-6 times/day)
Max dose	60 mg kg^{-1} day	60 mg kg^{-1} day (< 3 months) 80 mg kg^{-1} day (> 3 months)	90 mg kg^{-1} or 4 gr

Diclofenac, ibuprofen[42], idometacin and ketoralac are the most commonly used agents besides acetaminophen[43] in emergency.

Several other drugs (Table 3) have been studied to treat pain in children but a number of them are contraindicated in infants and very young children. Ibuprofen is effective in arthritis; perioperative administration of indometacin reduces opioid requirements; ketoralac is also effective in numerous situations, including children who have cystic fibrosis, rib fractures and children with sickle cell painful crisis.

Table 3: Recommended dose for NSAIDS and other sedatives in pediatric age

Drug	Dose	Advantages	Contraindications	Side effects
Diclofenac	*Oral or Rectal*: 0.3-1 mg kg^{-1} (3 times/day) *IV/IM*: 0.3-1 mg kg^{-1} (1-2 times/day) Max dose: 150mg/die	Pain treatment and inflammation (Juvenile arthritis)	Not neonates or infants <6 m Caution in asthma, rhinitis, gastric ulcer or renal /hepatic impairment, cardiac failure	Dyspepsia, nausea, diarrhea, bleeding and gastric ulcer; Headache, dizziness; Bronchospam Rush Fluid retention
Ibuprofen	*Oral*: Child < 25 kg: 5 mg kg^{-1} 6 hrly Child > 25 kg: 200 mg 8 hrly Max dose: 500 mg/day	Low / moderate pain treatment, fever, and inflammation	Not to be used in neonates, gastric ulcer, asthma and rhinitis Caution use in renal, hepatica and cardiac failure	Dyspepsia, nausea, diarrhea, gastric /intestinal bleeding Headache, dizziness; Bronchospam Rush Fluid retention
Ketorolac	*Oral or rectal*: 1 mg kg^{-1} *IV*: 0.5-1 mg kg^{-1} followed by 0.5 mg kg^{-1} every 6 h Max dose: 2 mg kg^{-1} day (90 mg/die) *IM*: is not to be preferred	Treatment of postoperative pain. Analgesic, antipyretic and inflammatory action	Higher gastrointestinal toxicity compared to other NAIDS Risk of bleeding in peri-operative phase for inhibition of platelets' aggregation	Dispnea, asthma Headache, dizziness; Euphoria, depression Dyspepsia, nausea, diarrhea, gastric /intestinal bleeding and pain
Indomethacin	*Oral / Rectal:* 1-2 mg kg^{-1} (2 times /day) Max dose: 200 mg/day	Moderate and severe pain and inflammation	Not to be used in peptic ulcer, asthma, rhinitis Caution use in renal, hepatica and cardiac failure	Headache, dizziness Bronchospam Pulmonary hypertension and intracranic bleeding Dyspepsia, nausea, vomiting diarrhea, gastric /intestinal bleeding and distention Rush Fluid retention

Bronchospasm induced by NSAIDs is very rare in children and asthma is not a contraindication to the use of NSAIDs. However NSAIDs should be avoided if the child has been recently or repeatedly hospitalized with asthma, or has required steroids systemically, or is known to be NSAID sensitive. Provocation of bronchospasm by NSAIDs is thought to be a result of a relative excess of leukotriene production.

Analgesia using opioids and natural or synthetic morphine-derivates

Opioids are considered the best way to control severe pain from different origins. They can be safely administered without fear of over-sedation and respiratory depression, provided the blood level of the opioid is maintained within a therapeutic range. Opioids may be used by oral, rectal, intravenous, or nasal routes according to the clinical status[44].

Adequate and better analgesia using these drugs should be given in a pre-emptive way. The use of opioids especially in continuous infusions gives rise to problems of tolerance, accumulation, withdrawal syndromes and possibly immuno-suppression. The longer term side effects of continuous exposure of neonatal central nervous system to opioids are not known and a better option may be to consider short term infusions to cover acutely painful episodes with regular reassessment between the level of sedation and analgesia required.

Morphine (Table 4)[45], meperidine, fentanyl, alfentanyl, sulfentanyl and remifentanil are the drugs must widely used (Table 5).

Fentanyl is a synthetic derivate of morphine, short acting after a single dose, but long elimination half-life because of rapid redistribution in the body. The effect of intravenous fentanyl administration in children is highly variable. Volume of distribution and total body clearance are greater than those reported in adults. Both these pharmaco-dynamic mechanisms appear to be responsible for the very prolonged respiratory depression[46-49].

Table 4: Recommended dose for morphine administration in neonates, infants and children

Route	Preterm neonate	Term neonate	Infant/children
Oral	---	---	0.3 mg kg^{-1} every 6 h
Rectal	---	---	0.3 mg kg^{-1} every 6 h
IM/SC	**Not recommended**	**Not recommended**	**Not recommended**
IV bolus	8 mcg kg^{-1} every 4 h	30 mcg kg^{-1} every 4 h	80 mcg kg^{-1} every 4 h
IV infusion	2 mcg kg^{-1} h	7 mcg kg^{-1} h	20 mcg kg^{-1} h
Epidural	Not recommended	Not recommended	30 mcg kg^{-1} h

Prolonged use of fentanyl may lead to dependence of the morphine type. Movement disorders, extreme irritability have been reported in children after withdrawal of prolonged fentanyl infusions.

Remifentanil is a potent ultra short-acting synthetic opioid analgesic drug. It is given to patients during surgery to relieve pain and as an adjunct to an anesthetic. Remifentanil is used for sedation as well as combined with other medications for use in emergency general anesthesia and in protected emergency area[50, 51].

Side effects of opioids

The sedative, respiratory depressant and analgesic effects of opioids can be antagonized by naloxone 2-4 mgkg^{-1} i.v. repeated to 10 mg/kg^{-1}. The duration of naloxone's effect is short and an infusion may have to be given to maintain reversal at a dose of 10 mg kg^{-1} h. Naloxone can be given i.m. in emergency in dose of 10 mg kg^{-1} [52, 53].

Cardiovascular and respiratory systems can be affected. Arterial and venous vasodilatation has been demonstrated by

Table 5: Morphine derived drugs

	Dose	Advantages	Disadvantages	Side effects
Fentanyl) (synthetic opioid)	*IV bolus:* 0.001 mg kg^{-1} *IV infusion* 0.002-0.005 mg kg^{-1} h *Oral transmucosal* dose: 0.010-0.015 mg kg^{-1}	More effective than morphine (70 to 125 times) to reduce stress hormones that occur in response to pain stimulus. Very effective for short, painful procedures	IV infusion: need for ventilatory support Coledocus spasm Not to be used in paraliticus ileus and feocromocitoma. Caution in the use in increased ICP and brain trauma. Oral transmucosal use is limited by nausea and vomiting. Dependence	Respiratory depression (concentration-dependent) Bradicardia, hypotension Chest and skeletal muscle rigidity Nausea,vomiting, stipsis. Itch Withdrawal syndrome in prolonged use
Sufentanil (synthetic opioid)	I.V.: 1-2 mcg kg^{-1} IV infusion: loading dose 0.2 mcg kg^{-1} followed by 0.05 mcg kg^{-1} h	1000 times as potent as morphine and 7 to 10 times more potent than fentanyl	Similar to fentanyl and remifentanil	Similar to fentanyl and remifentanil
Remifentanil (synthetic opioid)	IV infusion: 0.05 mcg kg^{-1} h (due to short action)	20-30 times more potent of alfentanil. Short onset action and short lasting side effects. Synergistic sedative and analgesic effects with propofol	Similar to fentanyl and sufentanil	Nausea, vomiting. Bradycardia, hypotension; Respiratory depression (concentration-dependent)
Codeine phosphate	*Oral*: 0.5-1 mg kg^{-1} (4- 6 times / day) Max dose: 240 mg	Low or moderate pain treatment Prescribed with acetaminophen	Not recommended < 3 months age and in hepatic and renal failure. Must never be given IV: hypotension occurs	Respiratory depression in neonate and infants Paralitic Ileum

having a direct effect on vascular smooth muscle. Vasodilatation is mediated by release of histamine. Postural hypotension may occur when a patient sits or stands. Bradycardia is vagally mediated. Opioids can reduce the sensitivity of brain stem respiratory centers to arterial CO_2 content. Ventilation can be affected by loss of airway tone causing upper airway obstruction (obstructive apnea), decrease in respiratory rate and tidal volume (hypoventilation) and/or changes in respiratory rhythm.

Several other organs and apparatus can be affected by uncontrolled or prolonged use of opioids. Nausea and vomiting are frequent and can be connected by stimulation of the chemoreceptor trigger zone in the medulla. Urinary retention may be present and could need for catheterization.

Tolerance, dependence, addiction and withdrawal syndrome have been largely described. Tolerance and physiological dependence develop with long term use. Patients may show a tolerance to opioids and need progressively larger doses. They can develop also tolerance to the respiratory depressant effects of opioids.

Signs and symptoms of withdrawal appear after 7-10 days if opioids are ceased abruptly and are

- Yawning, sweating, lacrimation, rhinorrhea;

- Anxiety, dilated pupils, pilo-erection, chills;

- Tachycardia, hypertension;

- Nausea and vomiting, cramps, abdominal pains and diarrhea.

Withdrawal symptoms can be prevented by daily tapered dose reductions of 20-25%.

Other analgesic and anesthetic agents (Table 6)

Tramadol is a synthetic phenil-piperidine analog of codeine and its use is suggested in pain treatment due to reduced side effects on respiration and hemodynamic. One of the major drawbacks of the use of tramadol is high incidence of nausea and vomiting, and urinary retention[54, 55].

Ketamine is an anesthetic agent which can be given by the oral, intravenous or intramuscular route. Since 1990, this drug has gained popularity for pediatric emergency department sedation because permits performing extremely painful procedures without the risk of cardio-respiratory depression. Ketamine dissociates the central nervous system from outside stimuli, thus producing a profound trancelike cataleptic state. The dissociative state is characterized by potent analgesia, sedation, and amnesia[56-58].

Ketamine tends to cause sympathetic nervous system stimulation and so blood pressure tends to remain stable or increase, intracranial pressure increases and elevated pulmonary pressure may rise further. Ketamine stimulates salivation and airway secretions and this may induce coughing and laryngeal spasm[59].

Ketamine is contra-indicated in patients in whom elevation of blood pressure would be a serious hazard and should be used with caution in patients with elevated CSF pressure. Verbal, tactile, and visual stimuli should be kept to a minimum during recovery to avoid hallucinations. The associated use with midazolam or diazepam will reduce hallucinations.

Propofol is a 2,6 diisopropylphenol widely used to induce general anesthesia but also emergency physician administered as sedation [60]. Even though controversies are still present in the use of this drug in young children for long sedation, the drug is used for short time sedation with excellent results due to the faster recovery profile. Children receiving propofol without mechanical ventilation must be closely observed because respiratory depression and hypoxemia are frequent complications. Propofol cannot be administered safely without provision for supplemental oxygen and artificial ventilation if necessary[61]. Propofol is not recommended for long term treatment under 8 years. In short term treatment can be used at dose 2-3 mg/ kg^{-1} h IV infusion.

There have been fatalities associated with prolonged infusion of propofol in PICU patients[62]. Progressive severe lactic academia and bradycardia unresponsive to conventional treatment in such a case has been successfully treated with continuous veno-venous hemofiltration.

Topic anesthesia

Topical anesthesia can be performed using a special emulsion cream such as EMLA. EMLA is eutectic mix of lignocaine 2.5% + prilocaine 2.5%. This cream is largely used when a needle is to be inserted, in lumbar puncture, in post-herpetic neuralgia, in routine immunization in children, and debridement of infected skin's ulcers.

Table 6: Drugs must widely used for anesthesia and analgesia

	Dose	Advantages	Disadvantages	Side effects
Tramadol	IM bolus: 0.75-1 mg kg^{-1} IV bolus:1-2- mg kg^{-1} :IV infusion: initial dose 0.25 mg kg^{-1} followed by dose adjusted individually (mean 0.21mg kg^{-1} h	Long time action. Efficacious in postoperative pain treatment. Not cardiovascular and respiratory depression, nor itch	Mediates sympathomimetic actions	Nausea, somnolence and sweating. Dysphoria and agitation by exceeding dose
Ketamine (dissociative agent)	*IV bolus* 0.5-2 mg kg^{-1} *IV infusion* 0.01-0.045 mg kg^{-1} h *IM:* 3-10 mg kg^{-1} *Oral:* 3-10 mg kg^{-1}	Induction/maintenance anesthesia, Sedation/Analgesia for painful procedures Not affect respiration. Stable pulmonary hemodynamic if $EtCO_2$ normal	Contraindicated in: - elevated ICP or IOP; - hypertension from different origin - active asthma - cardiac disease Nausea, unpleasant emergent reaction; Random movements and seizure disorders Not ideal for CT or MRI sedation	Hypersalivation, airway obstruction Age =12 months: laryngospasm; Apnea and respiratory depression if rapidly IV administration
Propofol (alkyl phenol)	IV bolus 1-2.5 mg kg^{-1} IV infusion (> 3 yrs) 9-15 mg kg^{-1} h For procedures: 1 mg kg^{-1} ev (in 1-5 min)	Titratable effects, rapid recovery **Not be used:** In intracranic endocranic and vascular brain problems	Sedation level may fluctuate unpredictably Hypotension in hypovolemic child Seizures in epileptic child Triglycerides increase	Pain at injection site; Bradycardia, hypotension; Apnea Nausea, vomiting, agitation

The cream should be applied to the skin with an occlusive dressing about 45 to 60 minutes prior to procedure for obtaining effective analgesia. Duration of analgesia is about one hour.

Local anesthetic gel 2% topically applied to the site of circumcision, and instilled onto or infiltrated into small open wounds are simple, safe, and effective techniques to control pain.

Local anesthesia

Surgical wound infiltration with lidocaine, bupivacaine or ropivacaine (0.25%) can be successful used to provide analgesia following skin biopsies, muscle biopsies and virtually all procedures where other regional blocks are either inappropriate or contraindicated. Particular attention can be reserved to accidental vessel puncture. In this case local anesthetic can cause toxic effects on the brain (seizures) and severe cardiotoxicity (bradycardia and cardiac arrest).

Final considerations

A progression in the treatment according to the needs of both patient and operator is

necessary in order to choose the most appropriate treatment for the specific requirement of the patient and to reduce side effects in emergency and immediately after. Prolonged analgesia must be titrated during the assessing phase (1-3 hours), the reassessing process for confirming analgesic efficacy and finally the re-evaluation of analgesic efficacy in order to highlight adverse effects and check on delivery system (e.g. bolus, continuous infusion). Intramuscular and subcutaneous injections must be avoided utilizing preferentially intravenous, rectal or oral routes of administration.

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