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ANALGOSEDATION IN PEDIATRIC POPULATION

Durnev V[1]

[1]University Clinic for Traumatology, Orthopedic Diseases, Anesthesia, Reanimation, Intensive Care and Emergency Centre, Medical Faculty, University "Ss. Cyril and Methodius," Skopje, Macedonia

Introduction

Almost all interventions and medical procedures cause great distress such as anxiety, fear and pain in children and their families. Achieving the optimal combination of adequate analgesic and sedation is a major challenge in this patients' population due to the wide spectrum of age, size and developmental stage.[1]

Under dosing increases the risk of physical and psychological stress that can have long-term consequences. Excessive sedation, on the other hand, increases the risk of side effects of analgesic and sedative agents, prolonged respiratory support, prolonged hospital stays or hospital admission. Both, insufficient analgosedation and overdose, put pediatric, especially critically ill patients at high risk of developing complications such as delirium, withdrawal syndrome, neuromuscular atrophy and weakness, post-traumatic stress and poor rehabilitation.
Optimal analgesia and sedation depend on continuous assessment with validated tools to help titrate analgesic agents.[2]

Many procedural procedures, such as endoscopy, computed tomography, bronchoscopy and magnetic resonance imaging are performed for the diagnostics and therapy of diseases. Also, everyday medical care involves blood sampling from venipuncture, nasogastric tube and urinary catheter placement, lumbar puncture, bone marrow aspiration etc.
All these invasive and inevitable investigation methods often represent a severe burden for children and can only be carried under anesthesia or sedation. Therefore, analgosedation is carrying great significance in the diagnostics and treatment in children to avoid psychological trauma and to optimize the results of the examination. [3]

Analgosedation can principally only be carried out by trained personnel who are capable of independently dealing with any complications that might occur. Prerequisites for dealing with complications are a good background knowledge on the pharmacokinetics and pharmacodynamics of the medications applied, the safe performance of basic and advanced cardiac life support in children, and the appropriate equipment. Complications rarely occur during sedation for diagnostic and therapeutic measures when a competent team takes care of the children based on predefined guidelines.

Pharmacodynamics and pharmacokinetics of analgesic and sedative agents

Clearance, metabolism and duration of drug effect, can be affected by dysfunction or insufficiency of the end organ (hepatic, renal, cardiac). The key factors affecting pharmacokinetics (PK) and pharmacodynamics (PD) can be divided into two elements: Patients' factors and factors resulting of the Pediatric Intensive Care Unit (PICU).[4, 5]

Patients'Factors

These factors include change in the redistribution of body fluids that affects the volume distribution of the drug, altered protein binding that may affect plasma drug concentration, and end-organ dysfunction that may alter drug absorption, metabolism and excretion. Other factors are natural age-related physiology that can affect drug absorption, metabolism, and excretion and inflammatory conditions that alter drug-metabolizing enzymes, as well as affecting drug absorption, efficacy and clearance.[6, 7]

PICU factors

Non-pharmacological interventions such as the use of continuous renal replacement therapy (CRRT), extra-corporeal membrane oxygenation (ECMO) and therapeutic hypothermia are belonging to PICU factors, all of which affect the extent of volume of distribution, metabolism, absorption and clearance.[8]

Analgesia

Effective, titrated treatment of acute, procedural and chronic pain, especially in PICU is essential tool for good patient's outcome.
The goal of analgesic therapy is to provide comfort, to reduce the physiological response to stress, to reduce adverse events associated with analgesics, such as respiratory depression, risk of dependence, hemodynamic instability and end-organ injury.
In the critically ill pediatric patient, this balance is delicate and, if failed, can predispose children to inappropriate pain management.[9]

Pain Assessment

In order to titrate analgesic therapy for adequate pain management, and monitor for signs of drug toxicity, or adverse effects, gold standard for monitoring the effectiveness of pain medication is patients' self-assessment scales. The premise of these scales is assigning a numeric value to the perception of pain, such as designating 0 as"nopain" and 10 as "worstpain".
Self-assessment is a good tool to detect the presence of pain, as well as the perceived intensity of pain. However, pain self-assessment can be challenging in some pediatric patients because of their limited ability to communicate (PICU patients) or comprehend as a result of age or disability.

Physiological indicators as tachycardia, rise in blood pressure, tachypnea, pupil dilation, increased muscle tone, sweating, etc. are unreliable signs because they lack pain sensitivity and

specificity. Behavioral signs of a child in pain, either verbal (vocalized description of intensity, quality, location with concomitant moaning or crying) or non-verbal (facial expression, body posture/repositioning, decreased activity) were also shown to be uncertain signs.[10]

In children <3 years, the standard for pain assessment is the use of behavioral observational pain scales using subjective and objective indicators that interpret facial expression and physiological and motor responses, often including the opinions of family members.

Children aged 4 to 8 years are usually able to self-report pain, so their subjective information is complemented by the application of an appropriate pain tool.

Older children (8 years and older) are usually able to self-assess their pain using more validated methods such as the verbal rating scale (VRS), numerical rating scale (NRS), and visual analog scale (VAS), similar to adults (11).[11]
Not all pain scales require self-assessment and interpretation of verbal cues. The Wong-Baker FACES scale and the Bieri Faces Pain Scale Revised (FPS-R) are suitable for children of any age and developmental stage and rely on nonverbal cues.
Each scale has its limitations. The observational scales as Neonatal Pain, Agitation, and Sedation Scale (N-PASS), Nonverbal Pain Scale (NVPS), and Face, Legs, Activity, Cry and Comfort (FLACC) scale cannot measure pain intensity or quality.

Table 1.FLACC Scale

	0	1	2
Face	Relaxed face, no particular Expression or smile.	Occasional grimace or scowl, retiring, disinterested.	Frequent to constant scowl, quavering chin,clenching jaw.
Legs	Normal position or relaxed.	Uncomfortable, restless, tense.	Kicking or legs pulled up.
Activity	Lying down quietly, normal position, moves easily.	Wriggling,shifting back And forth,tense.	Arched, rigid body or jerking.
Cry	No cry (awake or asleep).	Moans of whines, occasional compliant.	Crying consistently, screams or sobs, frequent complaints.
Consolability	Pleased, relaxed, not require consoling.	Reassured by occasional touching, clasping, or being talked to, distractible.	Inconsolable, difficult to comfort.
Total score 0=Relaxed and comfortable, 1–3=Mild discomfort, 4–6=Moderate pain, 7–10=Severe discomfort or pain or both. Adapted from Merkel SI *et al.*22			

Table 2. Comparison of Pain Assessment Instruments.

FLACC	Children, all ages	Acute, surgical	Observational	Behavioral,physiological
FPS-R	≥4years	Acute, surgical	Self	Pictorial
N-PASS	Neonates	Acute, surgical	Observational	Behavioral,physiological
NVPS	Children,all ages	Acute, surgical	Observational	Behavioral,physiological
NRS	≥6years	Acute, surgical, chronic	Self	Numeric
VAS	≥6years	Acute,surgical, chronic	Self	Numeric
Wong-Baker FACES	≥4years	Acute,surgical	Self	Pictorial

FLACC = Face, Legs, Activity, Cry, and Consolability scale; FPS-R = Faces Pain Scale Revised; N-PASS = Neonatal Pain, Agitation, andSedation Scale; NRS = numeric rating scale; NVPS = Nonverbal Pain Scale; VAS = visual analog scale.

Pain Treatment

Non-pharmacologicalTreatment

Non-pharmacological interventions include a range of so-called age-appropriate redirection techniques. Redirection techniques for infants include pacifiers, swaddling, rocking and holding. For older children, diversion techniques may vary but include using familiar toys, video games and television.

Other non-pharmacological interventions may include music or art therapy, a quiet environment with low stimulation and cognitive behavioral therapy.

The use of non-pharmacological therapies should always be considered and intertwined with pharmacological therapy.[12]

Pharmacological Pain Treatment

Pain assessment and identification of its underlying causes must lead to the choice of analgesic drug which must be of adequate power, and targeted to properly pain treatment.

Acute pain is the most frequent form of pain in PICU, but complex patients with prolonged stay in intensive care unit may present with persistent, chronic forms of pain, for which it may be necessary a multidrug combination.

The therapeutically schedule had to be daily reassessed according to the analgesic requirements. WHO's pain ladder, a step grading pain therapy still remains a valid method in treating pain by choosing drugs secondary to pain intensity.

Table 3. Analgesic drugs.

Drug	Intravenous bolus	Intravenous infusion	Per os
Morphine	Neonates - 25mcg/kg, Infants-children - 30-100mcg/kg.	Neonates - 5-10mcg/kg/h, Infants-children - 10-50mcg/kg/h.	Neonates - 80mcg/kg 4-6 hourly, Infants – children - 200-500mcg/kg/ 4 hourly.
Fentanyl	Neonates - 0.5-1mcg/kg, Infants-children - 1-2mcg/kg.	Neonates - 0.5-3mcg/kg/h. Infants-children - 1-5mcg/kg/h.	
Remifentanil		Neonates - 0.01-30.1mcg/kg/min, Infants-children - 0.02-1 mcg/kg/min.	
Paracetamol	Neonates - 7.5-10mg/kg 6-8 hourly max 30mg/kg/day, Infants (> 10kg) 15mg/kg 6-8 hourly max 60mg/kg/day, Children- (> 50 kg) 1g 6-8 hourly max 4g/day.		Neonates - 10-15mg/kg 8-12 hourly max 30mg/kg/day, Infants - 15mg/kg 4-6 hourly max 60mg/kg/day, Children – 15mg/kg 4-6hourly max 90mg/kg/day.
Ibuprofen Above 3 months			5-10mg/kg 6-8 hourly max 40mg/kg/day.

Recommendations:

- For children assessed as having mild pain paracetamol and non-steroidalanti-inflammatory drugs (NSAIDs) should be considered as the first options.
- For the treatment of severe pain, administration of opiates delivered by continuous intravenous infusions is recommended because of more accurate control of the dose and more steady plasma concentration.[13]
- Enteral route, when gastrointestinal motility and function are recovered, is also highly recommended.

- An iv analgesic drug may be administrated during oral route administration of analgesic treatment as adjuvant or rescue therapy.
- Paracetamol and nonsteroidal anti-inflammatory drugs in children above three months of age, and only paracetamol in neonates, are recommended for treating mild pain.
- Adding nonsteroidal anti-inflammatory drugsor paracetamol to opioids is useful to limit the total opioid dose required.
- Fentanyl is indicated in presence of cardiocirculatory instability, and in neonates with persistent pulmonary hypertension.

Loco-regional techniques must always be considered in cases of localized pain, such as procedures, surgery, trauma or burns. Ultrasound guided peripheral nerves block sare strongly recommended also in infants within 6months of age even if there is scarce evidence that ultrasound technique is more reliable than traditional land marking.[14]

- Epidural analgesia is effective for acute pain after surgery or trauma to the chest and abdomen.
- Use of EMLA in severe premature infants, mostly in repeated applications during the same day, carries the real risk of developing methemoglobinemia.

Sedation

The sedation targets are reduction of distress, fear, agitation, improvement of patient-ventilator synchrony and decrease in self-removing of invasive devices. Sedation cannot be implemented without an adequate analgesic treatment, since persistent not treated pain undermined the sedation strategy. Since standard sedation protocols suitable for all patients do not exist, one should be able to tailor sedative plan for each patient using minimal effective doses.[15]
Sedation is a particular challenge for anesthesiologists, nevertheless the pediatric patient is assigned for procedural sedation, or the patient is on mechanical ventilation in PICU.
The optimal condition for a patient who is breathing independently is that he wakes up easily, or is conscious, feels comfortable and breathes in synchronizing with the ventilator - the Goldilocks zone (not too deep and not too shallow). Balancing sedation to synchronize the patient with the ventilator is matter of mastering.
Balancing the depth of sedation is important because insufficient sedation can lead to dislocation of intravascular access and catheters, unplanned extubation, and potential injury to staff or the patient. Excessive sedation, on the other hand, can lead to unstable hemodynamics, respiratory depression, and possible extubation failure. Also, prolonged intubation poses an increased risk for muscle hypotonia, delirium, cognitive impairment, decreased tolerance and withdrawal syndrome.[16]

Table 4. Levels of sedation.

Level of sedation	Stimulus response	Airway	Ventilation	Hemodynamics

Minimal(“anxiolysis”)	Verbal and tactile	Unaffected	Unaffected	Maintained
Moderate(“consciouss edation”)	Verbal and tactile	Unaffected	Unaffected	Maintained
Deep	Noxious tactile	Affected	Affected	Maintained
Generalanesthesia	None	Affected	Affected	Impaired

Sedation Assessment

- State Behavioral Scale (SBS),
- COMFORT behavior scale,
- COMFORT-B scale,
- Richmond Agitation Sedation Scale (RASS).

State Behavioral Scale (SBS)

SBS monitors 8 parameters in mechanically ventilated children[17]:

1. Respiratory drive,
2. Response to ventilation,
3. Coughing,
4. Best response to stimulation,
5. Attention to the care provider,
6. Care tolerance,
7. It can be comforted,
8. Ability to move after comfort.

COMFORT Behavior Scale

The COMFORT behavioral scale is an observational scale that measures eight parameters to determine the level of distress of a critically ill child.[18]
Unlike the SBS, the COMFORT scale contains two physiological parameters and six behavioral dimensions:

1. Pulse,
2. Mean arterial pressure,
3. Alertness,
4. Calmness,
5. Respiratory response,
6. Movement,
7. Muscle tone,
8. Facial expression.

COMFORT BScale

The COMFORT-B scale eliminates both physiological parameters but adds excessive sedation and insufficient sedation. A limitation of this scale, however, is that scores of 10-23 are not predictive of adequate depth of sedation. The COMFORT-B scale is commonly used in conjunction with other observational scales. [19]

Richmond Agitation Sedation Scale (RASS)

The RASS is an agitation and sedation scale that has been validated for both adults and children (intubated and non-intubated) in the critical care setting.
The RASS is a 10-points scale ranging from 5 (unreactive) to +4 (combative) with 0 indicating readiness for increased attention and calmness.
For infants and children with cognitive or developmental limitations and for whom the level of alertness is difficult to assess, the original RASS is adapted to replace eye contact with eye opening when the RASS is -1 to -3.[20]
An important limitation of all these rating scales is their inability to be used for children with neuromuscular blockade.

Table 5. Initial Doses of Opioids and Sedatives in Children.

	Intermittent dose	Continuous intravenous infusion
Chloral hydrate	PO: 0.5–5mcg/kg	N/A
Clonidine	PO: 0.5–5mcg/kg	N/A
Dexmedetomidine	IN: 1–4mcg/kg IV: 0.5–1mcg/kg	0.2–0.7mcg/kg/hr
Etomidate	IV: 0.1–0.3mg/kg	N/A
Fentanyl	IN: 1–2mcg/kg IV: 0.5–3mcg/kg	0.5–2mcg/kg/hr
Hydromorphone	IV: 0.01–0.02mg/kg	0.003–0.005mg/kg/hr
Ketamine	IM: 5–10mg/kg	0.3–0.6mg/kg/hr
	IN: 3–5mg/kg	(5–10mcg/kg/min)
	IV: 0.5–3mg/kg	
	PO: 5–8mg/kg	
Lorazepam	IV: 0.05–0.1mg/kg PO: 0.05mg/kg	0.05mg/kg/hr
Midazolam	IM: 0.05–0.15mg/kg	0.03–0.12mg/kg/hr

	IN: 0.2–0.3mg/kg	
	IV: 0.05–0.1mg/kg	
	PO: 0.25–0.5mg/kg	
Morphine	IV: 0.03–0.2mg/kg	0.01–0.04mg/kg/hr
Pentobarbital	IM: 2–6mg/kg IV: 1–2mg/kg PO/PR: 1.5–6mg/kg	0.5–1mg/kg/hr
Propofol	IV: 0.5–2mg/kg	1.2–4.8mg/kg/hr (20–80mcg/kg/min)

Conclusion

Providing safe, effective and appropriate analgesia and sedation in children is challenging, complex and stressful intervention requiring experienced and well-trained personnel. However, the provision of analgesia and adequate level of sedation is frequently necessary to optimize the healing environment. Challenges with analgosedation in children include understanding of the pharmacokinetics and pharmacodynamics in pediatric patients, as well as how obesity and other illnesses contribute to medication pharmacokinetics. Analgesics and sedatives carry a high risk to imbalance the child homeostasis.

Appropriate analgosedation in children is hard to achieve. Over- or under-treatment are both harmful. Frequently, the reasons are lack of knowledge in pharmacological profiles of drugs and an insufficient applications of assessment tools.

Optimal analgesia and sedation are dependent on the implementation of validated tools to guide the titration of analgosedative agents, and screen for withdrawal and delirium. Optimal sedation should minimize physical and chemical restraints, encourage safe liberal activity, promote restorative sleep, and reduce the incidence of PICU-acquired complications (PACs).

References:

1. Chatham-Kent Health Alliance. Clinical Practice Manual. Procedural Sedation and Analgesia. Policy Number1-43-60.http://enw.org/Solutions.htm,underheadingProceduralSedation,documententitled:PolicyProceduralSedationandAnalgesia.(lastaccessed16July2010).

2. BaumanBH,McManusJGJr.Paediatricpainmanagementintheemergencydepartment.EmergMedClinNAm2005;23:393-414.

3. Mace SE, Barata IA, Cravero JP, et al. Clinical Policy: Evidence-based approach to pharmacologic agentsused in pediatric sedation and analgesia in the emergency department. Ann Emerg Med 2004;44:342-377.

4. Hughes, C.G.; McGrane, S.; Pandharipande, P.P. Sedation in the intensive care setting. Clin.

Pharmacol. **2012**, 4, 53–63. [CrossRef] [PubMed].

5. Varghese, J.M.; Roberts, J.A.; Lipman, J. Pharmacokinetics and pharmacodynamics in critically ill patients. Curr. Opin. Anaesthesiol. **2010**, 23, 472–478. [CrossRef].

6. Lu, H.; Rosenbaum, S. Developmental pharmacokinetics in pediatric populations. J. Pediatr. Pharmacol. Ther. **2014**, 19, 262–276.[CrossRef].

7. Fernandez, E.; Perez, R.; Hernandez, A.; Tejada, P.; Arteta, M.; Ramos, J.T. Factors and mechanisms for pharmacokineticdifferences between Pediatric population and adults. Pharmaceutics **2011**, 3, 53–72. [CrossRef].

8. Dzierba, A.L.; Abrams, D.; Brodie, D. Medicating patients during extracorporeal membrane oxygenation: The evidence isbuilding. Crit. Care **2017**, 21, 66. [CrossRef].

9. Hughes, C.G.; McGrane, S.; Pandharipande, P.P. Sedation in the intensive care setting. Clin. Pharmacol. **2012**, 4, 53–63. [CrossRef] [PubMed].

10. Playfor, S.D. Analgesia and sedation in critically ill children. Contin. Educ. Anaesth. Crit. Care Pain **2008**, 8, 90–94. [CrossRef].

11. Beckman, E.J. Analgesia and sedation in hospitalized children. In PedSAP 2017 Book 3: Sedation and Analgesia; The American College of Clinical Pharmacy: Lenexa, KS, USA, 2017; pp. 7–30.

12. Bushnell MC, Frangos E, Madian N. Non-pharmacological Treatment of Pain: Grand Challenge and Future Opportunities. Front Pain Res (Lausanne). 2021 May 28;2:696783. doi: 3389/fpain.2021.696783. PMID: 35295445; PMCID: PMC8915661.

13. WHOguidelinesonthepharmacologicaltreatmentofpersisting pain in children with medical illnesses. Geneva,WorldHealthOrganization,March2012.

14. Tsui B, Suresh S. Ultrasound imaging for regional anesthesia in infant, children, and adolescents. Anaesthesiology2010;112:719-28.

15. Hartman ME, McCrory DC, Schulman SR. Efficacy of sedation regimens to facilitate mechanical ventilation in thepediatric intensive care unit: a systematic review. PediatrCritCareMed2009;10:246-55.

16. Poh YN et al. Sedation guidelines, protocols, and algorithms in PICUs:a systematic review. Pediatr Crit CareMed 2014; 15: 885–892.

17. Curley, M.A.; Harris, S.K.; Fraser, K.A.; Johnson, R.A.; Arnold, J.H. State behavioral scale: A sedation assessment instrument forinfants and young children supported on mechanical ventilation. Pediatr. Crit. Care Med. **2006**, 7, 107–114.

18. Carnevale, F.A.; Razack, S. An item analysis of the COMFORT scale in a pediatric intensive care unit. Pediatr. Crit. Care Med. **2002**,3, 177–180.

19. Ista, E.; van Dijk, M.; Tibboel, D.; de Hoog, M. Assessment of sedation levels in pediatric

intensive care patients can be improvedby using the COMFORT “behavior” scale. Pediatr. Crit. Care Med. **2005**, 6, 58–63.

20. Sessler, C.N.; Gosnell, M.S.; Grap, M.J.; Brophy, G.M.; O’Neal, P.V.; Keane, K.A.; Tesoro, E.P.; Elswick, R.K. The richmondagitation-sedation scale: Validity and reliability in adult intensive care unit patients. Am. J. Respir. Crit. Care Med. **2002**, 166,1338–1344.