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**Analgesia in the palliative care of children**

Аналгезија у палијативном збрињавању деце

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## Analgesia in the palliative care of children

### Аналгезија у палијативном збрињавању деце

#### SUMMARY

Due to the increasing incidence of terminal illnesses in children, there is great urgency within pediatric medicine to give these patients the best palliative care possible. The main focus of palliative care is to alleviate suffering resulting from the psychophysical condition of the child, which is mostly due to physical pain. The first phase of managing pain in palliative care is quantifying and qualifying pain levels, although this is sometimes difficult to do with pediatric patients. In addition to implementing strategies that alleviate or remove pain for patients, it is also crucial to give patients and their families a feeling of full control over pain.

In practice, non-pharmacological and pharmacological methods of analgesia are present. Pharmacological methods include non-opioid and opioid analgesics, followed by co-analgesics as well as methods of regional anesthesia.

In order to give these patients the best care possible, it is necessary that the approach be individual, multimodal, multidisciplinary, and considerate of every detail.

**Keywords:** pain; palliative care; pediatric patients; analgesia

#### САЖЕТАК

Услед све већег пораста инциденце деце оболеле од неизлечивих болести, велики значај у педијатријској медицини је палијативно збрињавање ове деце. У основи палијативног збрињавања је пронаћи начин за ублажавање патње која произилази из психофизичког стања детета, а највећим делом произилази из бола. Понекад је изузетно тешко препознати, квантификовати и квалификовати бол код педијатријских пацијената, а то је управо прва фаза у проналажењу најбољег начина за ублажавање патње. Кључно је пронаћи најбољи начин за ублажавање или уклањање бола, али такође да то буде начин који ће како детету тако и родитељу пружити осећај потпуне контроле над болом.

У пракси су заступљене нефармаколошке и фармаколошке методе аналгезије. Фармаколошке методе укључују неопиоидне и опиоидне аналгетике, потом коаналгетике као и методе регионалне анестезије.

Да бисмо на најбољи начин збринули ову децу неопходно је да приступ буде индивидуалан, мултимодалан, мултидисциплинаран, и мора се посветити пажња сваком детаљу.

**Кључне речи:** бол; палијативно збрињавање; педијатријски пацијенти; аналгезија

#### INTRODUCTION

Terminal illnesses that affect children are a major issue within the medical community. Pediatricians are most often faced with malignant diseases where the survival rate is increasing, and where more than 80% of children diagnosed with malignant tumors can survive for more than 5 years due to advances in diagnostics, therapy, and supportive care [1]. By improving palliative care methods, pediatricians are able to increase the lifespans of these terminally ill children. Palliative care is defined by the World Health Organization as an 'approach to improve the quality of life of patients and families who face life-threatening illness, by providing pain and symptom relief, spiritual and psychosocial support from diagnosis to the end of life and bereavement [2]. Because pain is the main cause of anxiety, emotional, and behavioral problems with pediatric patients, the main focus of palliative care

is to prevent and stop pain, so that patients and their families can have a better quality of life [3, 4, 5].

The World Health Organization defines pain as an unpleasant sensory or emotional experience associated with actual or potential tissue damage [6]. According to this definition, it is clear that pain does not have to be linked to existing tissue damage and that emotional and cognitive components are an important component of the identification of pain. As a result, although this may be more difficult with younger children, patients should be encouraged to complain about pain in order minimize potential tissue damage [7, 8].

In order to create an effective treatment plan to stop and prevent the development of pain, pediatricians must account for the child's age, the psychophysical condition of the child, as well as the characteristic of the pain. The first step in treating pain is recognizing it, then qualifying and quantifying it. The second step is finding the best pharmacological and/or non-pharmacological method to treat the pain, and as such, pain therapy requires a multidisciplinary and multimodal approach [9–12].

## **TYPES OF PAIN IN CHILDREN**

Using pain duration as a basis, pain can be divided into two types: acute and chronic. Acute pain begins suddenly, is associated with a painful stimulus and is short-lived. Chronic pain can be the result of inadequately treated acute pain or may be chronic from the outset. Chronic pain significantly impairs quality of life.

Based on the pathophysiological mechanism of pain, pain is divided into nociceptive and neuropathic [13]. Nociceptive pain includes somatic and visceral pain. Somatic nociceptive pain is localized, constant, described as dull or sharp, worsens with movement, and is caused by tissue injury or inflammation. Visceral pain is caused by injury or inflammation of internal organs and can be constant if the pain originates from a solid organ, or intermittent in the form of cramps, or colic as a result of obstructions in hollow organs. Neuropathic pain is caused by injury, inflammation or dysfunction of the central or peripheral nervous system [14]. Patients may have mixed pain consisting of somatic, visceral, and neuropathic pain all at the same time or each separately at different times.

Breakthrough pain is a transient strengthening of a constant or controlled pain. There are three types of breakthrough pain: incidental, spontaneous, and pain at the end of a dosing interval [15, 16].

Cancer pain can also be acute and chronic. Acute pain is developed as a consequence of a tumor mass invading surrounding anatomical structures, which leads to their damage, compression, rupture, inflammation, or as a result of diagnostic and therapeutic procedures. Chronic pain is the consequence of the development of the tumor mass itself, metastases in other parts of the body, as well as a result of diagnostic and therapeutic procedures [17, 18].

Until recently, it was thought that neonates did not feel pain or feel less pain compared to older children and adults, but new research within the last decade has concluded that they do feel pain. In fact, fetuses can begin to feel pain from the 26th week of development [19].

#### **ASSESSMENT OF THE PAIN**

There are three basic methods for assessing pain: self-reporting, physiological indicators, and by observing the child's behavior. Often, there is a disagreement between objective estimates of the severity of the patient's difficulty and assessment, so the standard in assessing the existence of pain is to ask the child whether he/she feels pain (self-reporting) [20, 21]. In younger children can be difficult due to difficulties in understanding. Preschoolers may verbalize intensity of pain. School-age children may verbalize pain and use an objective measurement of pain. Adolescents should be able to locate and verbalize pain levels.

The second method of assessing pain is to measure physiological reactions to pain, which can be tracked through indicators such as pulse, blood pressure, breathing, redness, paleness, and increased sweating [22, 23].

The third method is observing the behavior of the patient, although this is not a specific pain indicator [24]. The behavior of the child must be interpreted in accordance with their age. Infants who feel pain will cry, scream, refuse food, sleep poorly, makes grimaces, or exhibit hypersensitivity or irritability. Facial expression measures appear most useful and specific in neonates. Toddlers may be verbally aggressive, cry, exhibit regressive behavior or

withdraw, guard painful areas of body, or be unable to sleep. Preschoolers may attempt to push a stimulus away before it is applied, be uncooperative, see the pain as a punishment, cling to a parent or nurse, or may request emotional support. School-age children experience nightmares related to pain, have muscular rigidity, exhibit body stiffness, closed eyes, wrinkled forehead, as well as engage in the same behaviors listed for preschoolers and toddlers. Adolescents may deny pain in the presence of peers, have changes in sleep patterns and appetite, or display regressive behaviors in the presence of their family.

## **PAIN SCALES**

The most used scales for newborns are the Premature Infant Pain Profile (PIPP) and the CRIES Postoperative Pain Scales [25, 26]. Between the ages of 2 months and 7 years the FLACC (Face, Legs, Activity, Cry, Consolability) scale is used for postoperative pain assessment [27]. Well established self-report pain scales for preschoolers include the Poker Chip Scale, Wong-Baker Faces Scale, and Faces Pain Scale-Revised (FPS-R) [28]. School-age children and adolescents can usually use verbal scales or visual analog pain scales (VASs) [29]. As for the assessment of pain for children with cognitive impairment, the Non-communicating Child's Pain Checklist – Postoperative Version is recommended [30, 31]. The greater the degree of cognitive impairment, the greater is the likelihood that the child feels less pain.

## **METHODS OF ANALGESIA**

Methods of analgesia include non-pharmacological and pharmacological methods that include the use of non-opioid and opioid analgesics with the use of co-analgesics or adjuvants, as well as methods of regional anesthesia. Developmental differences in response to pain and analgesic efficacy should be taken into account when planning analgesia [32].

## NON-PHARMACOLOGICAL METHODS

There is evidence that supports the use of psychological intervention for a variety of pain indications that include physiological, behavioral and cognitive techniques aimed at reducing pain and pain-related distress through the modulation of thoughts, behaviors, and sensory information [32]. Non-pharmacological methods include various ways of distracting the child's attention through cognitive methods, emotional support, presence of the parents during painful procedures, massage therapy, acupuncture, as well as physical techniques that promote muscle relaxation, transcutaneous electrical nerve stimulation (TENS), or hypnosis [33, 34]. The methods listed here are incredibly helpful and are seldom harmful.

## PHARMACOLOGICAL METHODS

In order to choose the appropriate medications and their doses, it is necessary to confirm that the child's organs are anatomically developed, although their organ function will not be fully developed until later on, as it takes 3 months for organs to reach maturity [35]. The most important factors to consider for the metabolism of drugs are immature liver enzymes and decreased renal function (reduced glomerular filtration) [36]. GFR has a range of only  $\frac{1}{2}$  of adult values at birth, and tubular secretion rates are only 20% of adult capacities. There are also some significant differences in the structure and function of the child's body at birth when they have a higher percentage of body water and less fat compared with older children. Age related differences in protein binding with drugs also exist. The effects of drugs may vary with age, and dosages must be changed to anticipate and avoid side effects [37].

Before administering analgesics, guidelines must be consulted and pediatricians must strive to achieve maximum efficacy with the chosen method of analgesia. According to the two-step scale of pain from the World Health Organization, the first stage of pain is mild, and it requires the administration of non-opioid analgesics like paracetamol or ibuprofen, with or without co-analgesics. The second stage of pain is moderate to severe, and opioid analgesics should be used with or without co-analgesics [38]. Drugs should be given according to a schedule, not on demand, because in practice this means that the child will not receive the medicine. The administration of the drug should try to be non-invasive, preferably given orally. Therapy must be individually adapted to each patient [38]. It is extremely important to

monitor the child and its reaction to the medication at all times, and if necessary, make changes to the therapy.

Non-opioid analgesics are used in the first stage of pain, according to the World Health Organization. Non-steroid anti-inflammatory drugs like ibuprofen and paracetamol are used. These medications work by blocking cyclooxygenase, where ibuprofen drugs work peripherally, while paracetamol leads to the central blockage of enzymes [39].

Opioid analgesics are used in the second, more severe, stage of pain. They can be administered orally, subcutaneously, intravenously, with a continuous infusion, or a PCA (patient controlled analgesia) pump [40]. The advantage of a PCA is that it eliminates high peaks and low troughs by allowing the patient to press the demand button when they begin to feel pain [41]. Opioid analgesics bind to opioid receptors in the central nervous system, but their usage requires monitoring because depression of the respiratory center can occur. Cardiorespiratory monitoring and observation is recommended when opioids are administered to infants less than 2-3 months of age.

## **NON-OPIOID ANALGESICS**

Paracetamol and ibuprofen are used to alleviate mild pain. For children up to three months of age, the only recommended drug for mild pain is paracetamol, while ibuprofen can be used with older infants. Routes for administration are oral (tablets, syrups), rectal (suppositories), or intravenously. Paracetamol is a well-tolerated drug and produces few side effects in the gastrointestinal tract, but there is a risk of hepatotoxicity and acute overdose [42, 43]. In addition having an analgesic effect, ibuprofen also has an anti-inflammatory and antithrombotic effect. Like the entire NSAID group of drugs, there are significant adverse effects for the mucosa of the gastrointestinal tract when ibuprofen is used [44]. There is a plateau for the analgesic effect of these drugs, but not for their side effects.

## **OPIOID ANALGESICS**

In cases of moderate to severe pain, there is a variety of opioid analgesics that can be used. Of opioid analgesics, morphine is always the medication of choice, while others are

considered and used when the side effects of morphine begin to appear [45]. Morphine is dosed gradually until pain is alleviated and there is no maximal dose because the pain acts as an antidote for respiratory depression, unlike non-opioid analgesics (Tables 1–4). Dosages should be adjusted to the patient following his/her pain level indication. The range of effective doses is very wide among children and can differ significantly for one child at different times. Opioid rotation is defined as the practice of changing between different opioids in a set schedule to prevent potential adverse effects and limit dose escalation [46]. The oral route of administration is recommended for the use of opioid analgesics, while the intramuscular route of administration is very unpleasant for children and should be avoided.

When administering opiates, the risks of tolerance, addiction, and withdrawal syndrome must be taken into consideration [47]. Tolerance to opioids occurs when the body becomes accustomed to a certain dose and an increased dose is required to obtain the same effect. Addiction is the creation of psychological and physical dependence on a drug, creating an irresistible need to take the medication again, regardless of possible consequences. Withdrawal syndrome is characterized by symptoms like agitation, insomnia, tremors, gastrointestinal symptoms like nausea, vomiting, poor appetite, tachycardia, tachypnea, hypertension, and fever. Children who have been on opiates for a long time and at high dosages require gradual reduction of opiate use in order to prevent the development of addiction. If opioid therapy lasted for 7–14 days, the dose can be decreased by 10–20% of the original dose every 8 hours. In the case of a long-term therapy protocol, the dose should not be reduced more than 10–20% per week [38]. When opioid overdose occurs, central respiratory depression develops, which can lead to a coma. Naloxone can be administered to a patient to stop the immediate opioid overdose, but opioid addiction and the development of withdrawal syndrome cannot be cured by Naloxone, so further treatment will be needed to treat the addiction [48].

### **ADJUVANT-COANALGESICS**

Co-analgesics have a primary purpose other than pain management, but they can be used in addition to analgesics to better control pain relief. Corticosteroids, bisphosphonates, antidepressants, anticonvulsants, and ketamine can be used as co-analgesics, but there are still no recommendations for their use in pediatric patients.



## METHODS OF REGIONAL ANESTHESIA

The application of regional anesthesia in childhood depends on the physiological specifications of their age, as well as by the technical capabilities of the anesthesiologist [49]. The effect of the block is short-term, and for long-term effects, catheter techniques are used. The use of catheter techniques improve the control of postoperative pain, reduces the use of analgesics and opioids, postoperative nausea and vomiting, time spent in the hospital, as well as costs, all of which improves the satisfaction of the patients and their families with the procedure [50].

## CONCLUSION

The primary goal of treating terminally ill children of all ages is giving them life without pain. It is necessary to keep in mind that a child often cannot adequately interpret the pain he/she feels, so it is necessary to monitor the child at all times and adjust the therapy accordingly. Pain therapy in palliative care should always be multimodal and multidisciplinary because this will improve efficacy and minimize side effects.

**Conflict of interest:** None declared

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**Table 1.** Non-opioid analgesics for the relief of pain in neonates, infants, and children according to WHO recommendations [32]

Dose (oral route)				
Medicine	Neonates 0–29 days	Infants from 30 days to 3 months	Infants 3–12 months or children 1–12 years	Maximum daily dose
Paracetamol	5–10 mg/kg every 6–8 hrs <sup>a</sup>	10 mg/kg every 4–6hrs <sup>a</sup>	10–15 mg/kg every 4–6 hrs <sup>a,b</sup>	Neonates, infants and children max 4 doses/daily
Ibuprofen	/	/	5–10 mg/kg every 6–8hrs	Child: 40 mg/kg

<sup>a</sup>Children who are malnourished or in a poor nutritional state are more likely to be susceptible to toxicity at standard dose regimens due to reduced natural detoxifying glutathione enzyme;

<sup>b</sup> maximum of 1 g at a time

**Table 2.** Starting dosages for opioid analgesics for opioid-naive neonates according to WHO recommendations [32]

Medicine	Route of administration	Starting dose
Morphine	IV injection <sup>a</sup>	25–50 mcg/kg every 6 hrs
	SC injection	
	IV infusion	Initial IV dose 25–50 mcg/kg, then 5–10 mcg/kg/hr 100 mcg/kg every 6 or 4 hrs
Fentanyl	IV injection <sup>b</sup>	1–2 mcg/kg every 2–4 hrs <sup>c</sup>
	IV infusion <sup>b</sup>	Initial IV dose 1–2 mcg/kg, then 0.5–1 mcg/kg/hr

<sup>a</sup>Administer IV morphine slowly over at least 5 minutes;

<sup>b</sup>intravenous doses for neonates are based on acute pain management and sedation dosing information; lower doses are required for non-ventilated neonates;

<sup>c</sup>administer IV fentanyl slowly over 3–5 minutes

**Table 3.** Starting dosages for opioid analgesics in opioid-naive infants (1 month – 1 year) according to WHO recommendations [32]

Medicine	Route of administration	Starting dose
Morphine	Oral (immediate release)	80-200 mcg/kg every 4 hrs
	IV injection <sup>a</sup>	1–6 months: 100 mcg/kg every 6 hrs
	SC injection	6–12 months: 100 mcg/kg every 4 hrs (max 2.5 mg/dose)
	IV infusion <sup>a</sup>	1–6 months: initial IV dose: 50 mcg/kg, then: 10–30 mcg/kg/hr 6–12 months: initial IV dose: 100–200 mcg/kg, then: 20–30 mcg/kg/hr
Fentanyl <sup>b</sup>	SC infusion	1–3 months: 10 mcg/kg/hr 3–12 months: 20 mcg/kg/hr
	IV injection	1–2 mcg/kg every 2–4 hrs <sup>c</sup>
Fentanyl <sup>b</sup>	IV infusion	Initial IV dose 1–2 mcg/kg <sup>c</sup> , then 0.5–1 mcg/kg/hr
	Oxycodone	Oral (immediate release)

<sup>a</sup>Administer IV morphine slowly over at least 5 minutes;

<sup>b</sup>intravenous doses of fentanyl for infants are based on acute pain management and sedation dosing information;

<sup>c</sup>administer IV fentanyl slowly over 3–5 minutes

**Table 4.** Starting dosages for opioid analgesics in opioid-naive children (1–12 years) according to WHO recommendations [32]

Medicine	Route of administration	Starting dose
Morphine	Oral (immediate release)	1–2 years: 200–400 mcg/kg every 4 hrs 2–12 years: 200–500 mcg/kg every 4 hrs (max 5 mg)
	Oral (prolonged release)	200–800 mcg/kg every 12 hrs
	IV injection <sup>a</sup>	1–2 years: 100 mcg/kg every 4 hrs 2–12 years: 100–200 mcg/kg every 4 hrs (max 2.5 mg)
	SC injection	
	IV infusion	Initial IV dose : 100–200mcg/kg <sup>a</sup> , then 20–30 mcg/kg/hr
SC infusion	20 mcg/kg/hr	
Fentanyl	IV injection	1–2 mcg/kg <sup>b</sup> , repeated every 30–60 minutes
	IV infusion	Initial IV dose 1–2 mcg/kg <sup>b</sup> , then 1 mcg/kg/hr
Hydromorphone <sup>c</sup>	Oral (immediate release)	30–80 mcg/kg every 3–4 hrs (max 2 mg/dose)
	IV injection <sup>d</sup> or SC injection	15 mcg/kg every 3–6 hrs
Methadone <sup>e</sup>	Oral (immediate release)	100–200 mcg/kg every 4 hrs for the first 2–3 doses, then every 6–12 hrs (max 5 mg/dose initially) <sup>f</sup>
	IV injection <sup>g</sup> or SC injection	
Oxycodone	Oral (immediate release)	125–200 mcg/kg every 4 hours (max 5 mg/dose)
	Oral (prolonged release)	5 mg every 12 hours

<sup>a</sup>Administer IV morphine slowly over at least 5 minutes;

<sup>b</sup>administer IV fentanyl slowly over 3–5 minutes;

<sup>c</sup>hydromorphone is a potent opioid and significant differences exist between oral and intravenous dosing; use extreme caution when converting from one route to another; when converting from parenteral hydromorphone to oral hydromorphone, doses may need to be titrated up to 5 times the IV dose;

<sup>d</sup>administer IV hydromorphone slowly over 2–3 minutes;

<sup>e</sup>due to the complex nature and wide interindividual variation in the pharmacokinetics of methadone, methadone should only be used by practitioners experienced with its use;

<sup>f</sup>methadone should initially be titrated like other strong opioids; the dosage may need to be reduced by 50% 2–3 days after the effective dose has been found to prevent adverse effects due to methadone accumulation; from then on, dosage increases should be performed at intervals of one week or more and with a maximum increase of 50%;

<sup>g</sup>administer IV methadone slowly over 3–5 minutes