SPECIAL ARTICLE

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Guidelines for treatment of acute pain in children – the consensus statement of the Section of Paediatric Anaesthesiology and Intensive Therapy of the Polish Society of Anaesthesiology and Intensive Therapy

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RATIONALE AND SCOPE OF THE GUIDELINES

Pain is a subjective unpleasant sensory and emotional experience. Acute pain occurs irrespective of age and has a prevalence of about 5% of the general population. Surgical procedures and painful diagnostic procedures are the main causes of this unpleasant and dangerous phenomenon for hospitalized children. It should be remembered that maintaining homeostasis in a child undergoing surgery is also affected by provision of an adequate level of analgesia and sedation as well as nerve conduction block within the surgical site. Even though both paediatric anaesthesiologists and paediatric surgeons know that the therapeutic activities during the perioperative period should be focused on ensuring sufficient analgesia and haemodynamic stability in surgical patients, as many as 70% of children undergoing surgery may experience moderate to severe pain [1–7].

Moreover, pain management is one of the fundamental human rights, i.e. the right to relief of suffering. According to the declaration of the 13th World Congress on Pain in Montreal (September 2010), this right also includes children [8, 9]. In Poland, the law was amended in 2017, and now each patient is guaranteed the right to relief and treatment of pain (Journal of Laws of 2017, item 836). Unfortunately, this right is not always respected in paediatric patients.

Many factors contribute to ineffective analgesia in paediatric patients, mainly insufficient knowledge and lack of experience (concerning the use of opioids in particular), as well as lack of management standards, the negative attitude of the personnel or poor organization [10–13]. In hospitals which, as a result of organizational changes, have implemented analgesic treatment regimens and regularly educate their personnel in these issues, both efficiency and effectiveness of pain relief in children are high [14].

For many years, Polish paediatric anaesthesiologists have been promoting and streamlining the analgesic management of children, which has led to the development of the present publication. The regimens presented in it are based on both the latest medical reports and many years of the authors' experience. The classes of recommendations and levels of evidence have been prepared (Tables 1 and 2, respectively). The presented recommendations were formulated based on a survey of medical reports published in the last two decades.

CONSEQUENCES OF NOT TREATING PAIN IN CHILDREN

In humans, the processes of central nervous system (CNS) maturation take a very long time (up to the age of 27–28 years), yet their highest activity is observed during pregnancy and in the first

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TABLE 1. Classes of recommendations

Class of recommendations	Definition
Class I – is recommended/is indicated	Scientific evidence and/or general agreement that a given therapeutic procedure is beneficial, effective and useful
Class II – to be considered	Conflicting evidence and/or divergent opinions on usefulness/effectiveness of a given therapeutic procedure
Class IIa – should be considered	Weight of evidence/opinions is in favour of usefulness/efficacy
Class IIb – may be considered	Usefulness/effectiveness is less well established by evidence/opinions
Class III – not recommended	Evidence or consensus that a given therapeutic procedure is useless/ineffective, and in some cases may be harmful

TABLE 2. Levels of evidence

Level A	Data derived from many randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized clinical trial or large non-randomized studies
Level C	Consensus of opinion of experts and/or data derived from small studies, retrospective studies, registers

two years of life. The process of nerve fibre myelination starts in the fifth month of pregnancy; prior to the child's birth, it involves only the fibres running through the hypothalamus and subcortical nuclei. This process, successively involving the pyramidal tracts and the reticular system, is continued in the first years of life and terminates at about 20 years of age in the association fibres of the cerebral cortex. Chronic pain stimulation in the early years of life is a factor which may impair the CNS maturation processes and significantly modulate pain behaviours in the later stages of life [15–17]. It has been demonstrated that insufficient analgesia in the neonates undergoing surgery or painful procedures while hospitalized in the intensive care unit (ICU) results in lowering their pain threshold in the future [18–21]. Another extremely important consequence of untreated acute pain in children is the risk of developing chronic pain. It is believed that the prevalence of pain in children is comparable to that in adult patients. There is evidence that severe pain persisting longer than 2 weeks postoperatively is a risk factor for developing chronic pain within a year [22–24].

SAFETY OF ANALGESIA

Most of the adverse events related to analgesia in children are due to human errors during prescribing, dispensing and administering analgesics, as well as incorrect assessment of the patient's condition [1–4].

To ensure that analgesia in the hospital setting is safe and effective, correct preoperative education is required (of the personnel as well as children and their parents/legal guardians). Other necessary conditions to be met are: planning of perioperative pain management, good knowledge of analgesics, including their dosage, contraindications and adverse side effects, as well as proper patient supervision (correctness of medical orders, i.e. the dose, route of administration, intervals between doses, communication with the nursing staff executing the doctor's orders), child monitoring during the provision of analgesia, keeping medical records (formulation and implementation of analgesia protocols), regular pain assessment, monitoring for adverse reactions and regular training for the medical personnel.

One of the relevant elements of effective analgesic therapy is the provision of clear information to the child and parents/legal guardians about the planned pain management procedures, informing them how the pain should be reported and assessed. An individualized approach to perioperative analgesia should involve preoperative evaluation of the patient, including history and physical examination. Administration of analgesics should be tailored to the patient's individual needs.

BASIC PRINCIPLES OF ASSESSMENT AND MEASUREMENT OF PAIN INTENSITY

Regular pain measurement and assessment is recommended in children – *recommendation I A.*

Children experience pain in a similar way to adults. Pain intensity in children depends on the surgical procedure itself but also on numerous other factors such as age, emotional state or the level of anxiety associated with the hospital stay. Previous pain experiences or chronic diseases that required many medical procedures may significantly change the pain threshold in paediatric patients. Moreover, genetic predispositions and environmental effects are significant [25]. Assessment of pain intensity in a child is a fundamental condition for postoperative pain management to be effective. Pain intensity control enables effective analgesia and reduces the risk of excessive and unnecessary drug administration.

In neonates, infants and young children, pain assessment is difficult because of the lack of verbal communication with them. Commonly recognized pain signs, such as motor agitation, uninterrupted

screaming, distressed facial expressions, tachycardia or increased arterial blood pressure, may not be present or may be limited due to the patient's general condition. Some of the above symptoms may be expressions of anxiety caused by factors other than pain, e.g. discomfort, feeling cold or hungry.

Unfortunately, there are still no universal tools for pain assessment that could be used in all children; therefore, the available tools should be adjusted to individual age groups. The scales most commonly used in young children rely on pain assessment conducted by the medical personnel and mainly involve the assessment of their behaviour, e.g. FLACC (Face, Legs, Activity, Cry and Consolability) and/or physiological parameters, e.g. CRIES (Crying, Requirement for O_2, Increased heart rate, Expression, Sleeplessness). In older children, it is possible to use self-report scales, e.g. the VAS (Visual Analogue Scale), the NRS (Numeric Rating Scale), or the FACES Pain Rating Scale (Tables 3 and 4). Some of the scales enable not only recognition of pain but also determination of its intensity [26–38]. The simplest and most common classification of pain intensity divides it into three levels: mild – 1–3 VAS/NRS/FLACC points; moderate – 4–6 VAS/NRS/FLACC points; and strong/severe – 7 or more VAS/NRS/FLACC points. It should be remembered that pain intensity has to be assessed both at rest and in dynamic conditions, e.g. during coughing, deep breathing, or walking. According to the VAS/NRS/FLACC scales, pain intensity should not exceed 4 points at rest, and 6 points in dynamic conditions. Pain treatment should aim at complete pain relief, or, if not feasible, at achieving a pain intensity bearable for the patient.

Provision of adequate analgesia in children is consistent with the protocols for comprehensive perioperative care to improve treatment outcomes – Enhanced Recovery After Surgery (ERAS) in paediatrics [40–45].

TABLE 3. Pain intensity rating scales in children

Scales based on self-report	
FACES Scale (Wong-Baker) – for those aged 3 to 18 years (the scale consists of 6 drawings of facial expressions; each face is scored 0–5 or 0–10) **Faces Pain Scale – Revised** – for those aged 4 to 12 years (the scale consists of 6 drawings of face expressions; an examiner gives 0, 2, 4, 6, 8 or 10 points to faces indicated by the child (counting from left to right) **VAS Scale (Visual Analogue Scale)** – for those aged 3 to 18 years (the VAS scale is a 10 cm line with 0 meaning total absence of pain, and 10 meaning the worst pain imaginable **NRS Scale (Numeric Rating Scale)** – for those aged 3 to 18 years (scale from 0 to 10, where 0 means *I'm not feeling any pain*, and 10 means *the worst pain imaginable*) **Pieces of Hurt Tool Scale**– for those aged 3 to 18 years	
Scales based on child's behaviour or behaviour and physiological parameters	
Children and adolescents without cognitive impairment	**FLACC Scale (Face, Legs, Activity, Cry, and Consolability)** – for those aged 1 to 18 years **PPPM Scale** (Parents' Postoperative Pain Measure) **COMFORT scale** (behavioural and physiological parameters)*
Children and adolescents with cognitive impairment	**NCCPC-PV Scale (Non-Communicating Children's Pain Checklist – Postoperative Version)** – for those aged 3 to 18 years **PPP Scale (Paediatric Pain Profile)** – for those aged 1 to 18 years **FLACC Scale-Revised (Face, Legs, Activity, Cry, and Consolability)** – for those aged 4 to 18 years **INRS (Individualized Numeric Rating Scale)** – for those aged 3 to 18 years

*Presented in Table 4

TABLE 4. Pain intensity rating scales in neonates

Scale	Parameter	Outcome	Application
Premature infant pain profile (PIPP)	Age from conception, behaviour, pulse, haemoglobin oxygen saturation, raising eyebrows, tightening of eyelids, nasolabial sulcus	Number of points to score: 0–21 Each parameter scored 0–3 points Minimal pain ≤ 6, moderate-to severe pain > 12	Procedural and postoperative pain
FLACC (Face, Legs, Activity, Cry, and Consolability)	Facial expression, leg position, activity, cry, possibility of consoling	Number of points to score: 0–10 Each parameter scored 0–2 points Moderate pain > 4, severe pain > 7	Procedural and postoperative pain
COMFORT scale (behavioural and physiological parameters)	Wakefulness, mood, reaction to ventilator breathing, ambulation, muscle tone, facial expressions, MAP, HR	Number of points to score: 8–40 Each parameter scored 1–5 points Sufficient sedation 17–26, insufficient sedation/analgesia > 27	Pain and sedation in neonatal intensive care unit
CRIES (Crying, Requirement for O_2, Increased heart rate, Expression, Sleeplessness)	Cry, demand for additional oxygen supply for saturation > 95%, vital signs, facial expressions, sleep patterns	Number of points to score: 0–10 Each parameter scored 0–2 points Moderate pain > 4, severe pain > 7	Postoperative pain in neonatal intensive care unit

It includes an obligation to assess pain intensity on a regular basis, i.e. at least 3 times a day, and to keep records of assessments (similarly to other vital signs).

Recently developed devices for pain monitoring and measurement give hope that pain assessment will be optimized, especially in the youngest children and those hospitalized in ICUs. Some of the devices rely on the analysis of heart rate variability, while others rely on changes in the state of parasympathetic system by measuring the changes in skin transduction [39] (*recommendation II C*).

Other methods of objective pain measurement based on determinations of plasma concentrations of such nociceptive markers as cortisol, catecholamines, growth hormone, etc., are not applicable in children due to their invasiveness.

BASIC PRINCIPLES OF PAIN MANAGEMENT IN CHILDREN

General principles of acute pain management in children:

1. When choosing a method of analgesia, the child's age, previous pain experiences, type of surgery, expected pain intensity and duration should be considered [46, 47] (*recommendation I C*).
2. In paediatric patients, analgesics are administered at equal intervals according to age-related pharmacokinetics of drugs, or in continuous infusions, which allows a constant blood concentration of analgesics to be maintained and effective analgesia to be provided [46, 47] (*recommendation I C*).
3. It should be remembered that in correctly conducted analgesia, drugs are not administered on demand. In the case of breakthrough pain, rescue doses of analgesics are applied. In children, analgesics should be administered with consideration, which means that the intramuscular route should be eliminated [46, 47] (*recommendation I C*).
4. The route of analgesic administration should be comfortable primarily to the child; therefore, certain conditions should be considered, e.g. the child's current swallowing capabilities, or presence of an intravenous line (maintaining vascular access in the youngest children after surgery is often difficult, if not impossible, since its presence by itself may cause discomfort in the child). Intravenous and oral routes of analgesic administration are most common in children [46, 47] (*recommendation I C*).
5. When the intravenous route of administration has been chosen, the following methods may be used: single doses of analgesics repeated at equal intervals, and continuous infusions, including the commonly used PCA (patient-controlled analgesia) or the NCA method (nurse-controlled analgesia) preferable in paediatric intensive care units (PICUs) [46, 47] (*recommendation I C*).
6. In paediatric postoperative analgesia, continuous subcutaneous supply of analgesics is recommended (e.g. morphine) (*recommendation I A*). This route is intended particularly for oncological/hospice patients. The use of transdermal patches is acceptable (*recommendation I C*) [46, 47].
7. In the youngest children, if an analgesic cannot be administered orally or intravenously, rectal administration is acceptable [46, 47]. However, this route should be avoided in immunosuppressed children due to the risk of developing perianal abscesses (*recommendation I C*).
8. Alternative routes of administration of analgesics include nasal or transmucosal supply (buccal, sublingual), which can be used in certain situations [46, 47] (*recommendation I C*).
   Nasal supply of medications is an attractive way of controlling severe pain in children, especially when intravenous access cannot be achieved or is undesirable (hospice care at home, burns, painful dressing changes). The nasal route may be used to administer potent opioids such as fentanyl, sufentanil and ketamine. The doses are usually twice as high as the intravenous doses. Even though preparations for nasal opioid supply are available in Poland (e.g. fentanyl), they are not approved for use in children.
9. Proper postoperative analgesia in children should include correct assessment of pain intensity, knowledge of pharmacology of analgesics used in different age groups and the ability to perform conduction (regional) anaesthesia techniques, if feasible [46, 47] (*recommendation I C*).
10. Severe pain in children should be prevented by providing pre-emptive analgesia that may result in lowering the postoperative pain intensity, thereby reducing the patient's requirements for analgesics [48–51] (*recommendation I B*).
11. Injecting the surgical wound with a local anaesthetic (LA), preferably prior to performing an incision or at least before the surgery is finished, is a significant complement of perioperative pain management [52, 53] (*recommendation I B*).
12. The possible use of non-pharmacological methods (distraction methods), such as fairy tales, films or toys, should be considered, which can help redirect the child's attention to things not connected with his/her current condition [54, 55] (*recommendation I C*).

MULTIMODAL ANALGESIA

Pain management in children should be based on the principles of multimodal analgesia – *recommendation I A*.

Multimodal analgesia is a fundamental principle of pain management in children according to which

drugs and techniques targeted at different mechanisms of providing analgesia, transduction and perception of nociceptive stimuli should be combined to achieve desirable results. In multimodal analgesia, the synergistic effects of different analgesics ensure effective analgesia, thereby minimizing the risk of side effects. This method of analgesia combines the use of analgesics, co-analgesics and regional or local anaesthetic techniques [56–58].

PHARMACOTHERAPY OF PAIN

Opioid analgesics

Opioids should be used for pain management in children – *recommendation I A*.

Opioids are analgesics commonly used in children, mainly for relieving moderate to severe pain. Mu opioid receptor (μ-receptor) agonists are most frequently used in the treatment of acute pain in children. They exert an analgesic effect and affect mood, behaviour, respiratory, cardiovascular, and digestive functions as well as functioning of the neuroendocrine and immune systems. The most common opioid-induced side effects include nausea, vomiting, excessive sedation, constipation, urine retention, itching and respiratory depression.

Bearing in mind the risk of potential side effects, a possible combination of opioids with other analgesics for pain management in children is noteworthy. Their synergistic or additive effects may reduce the total postoperative opioid dose, thus reducing the probability of side effects. An increasing number of reports point to adverse aspects of opioid effects: an immunosuppressive effect, possible opioid-induced hyperalgesia or increased tolerance to opioids. Such an 'opioid paradox' may occur in the case of ultra-short-acting opioids. This effect is manifested by increasing pain intensity despite opioid dose escalation.

In the perioperative period, the intravenous route of opioid administration is most common. However, other routes of administration are also possible, e.g. subcutaneous, oral or transdermal, which allows unconventional therapy to be planned. When opioids are administered in a continuous infusion, strict and continuous monitoring of the patient's vital signs is necessary due to the risk of respiratory depression.

Morphine is a μ-receptor agonist considered the gold standard against which the effects of all other opioids are compared. Its pharmacokinetics in children is similar to that in adults, except for premature babies and neonates, in whom morphine doses should be reduced due to their immature livers and kidneys [59–61]. Exceeding the dose is likely to cause accumulation of the active metabolite of morphine (morphine-6-glucuronide), which may result in respiratory failure [62–64]. Age-dependent pharmacokinetic parameters of morphine are presented in Table 5.

TABLE 5. Age-dependent pharmacokinetic parameters of morphine

	Vd (L kg^{-1})	$t_{1/2}$ (h)	CL (mL min^{-1} kg^{-1})
Premature babies	–	9.0 ± 3.4	2.2 ± 0.7
Neonates	2.8 ± 2.6	6.5 ± 2.8	8.1 ± 3.2
Infants and children	–	2.0 ± 1.8	23.6 ± 8.5
Adults	–	2.1 ± 0.9	38.0 ± 5.3

Vd – volume of distribution, $t_{1/2}$ – half-life, CL – clearance

For acute pain relief in children, morphine may be used outside the PICUs, provided that extreme caution and diligence are exercised and the patient's vital signs are continuously monitored.

Sufentanil is an opioid which is 1,000 times more potent than morphine and 10 times more potent than fentanyl. Its safe use should be confined to the PICU setting. It is preferably administered in a continuous infusion, although single doses may be administered as required (*pro re nata* – PRN).

Oxycodone is an agonist of μ, κ, and δ receptors with strong analgesic effects. The asset of this drug is its availability in intravenous and oral forms. In Poland, oxycodone has been approved for children over 12 years of age.

Sequential therapy involves replacing the parenteral form of a drug with its oral form once its effective dose has been determined and the patient's clinical condition has improved. In sequential therapy, drugs well absorbed from the gastrointestinal tract and characterized by high bioavailability are in use. Both morphine and oxycodone may be applied in sequential therapy in children. The ratio used to convert a morphine parenteral dose into an oral dose is 1 : 3; for oxycodone this ratio is 1 : 2.

In recent years, agonist/antagonist drugs have found a special place in paediatric analgesia. Their characteristic feature is the "ceiling effect", which means that dose escalation does not increase the risk of respiratory failure. Unfortunately, increasingly high doses do not increase the effectiveness of pain treatment. Due to the "ceiling effect", agonist/antagonist drugs are used for managing mild to moderate postoperative pain.

Nalbuphine, one of the drugs from this group used most frequently, is an agonist of the κ receptor and an antagonist of the μ receptor [65]. It is recommended for relieving pain of mild to moderate intensity and is usually administered intravenously, at a dose of 0.1–0.2 mg kg^{-1} every 3–6 hours, or in an infusion at 0.05–0.1 mg kg^{-1} h^{-1} [66].

The theoretical limitation of this group of drugs is their antagonistic effect on the μ receptor, which lowers the effectiveness of analgesia performed with rescue doses of full agonists and makes titration of the effective dose necessary.

However, it is worth noting that reports published recently have documented the additive effect of combining morphine with nalbuphine in managing postoperative pain [67].

Tramadol is another weak opioid. It is an agonist of the μ, δ and κ receptors showing a specific affinity for the μ receptor.

Moreover, its analgesic effect results from noradrenaline reuptake inhibition and increased serotonin release.

Considering the increased risk associated with the use of tramadol in the population of paediatric patients, in 2018, the United States Food and Drug Agency (FDA) forbade its use in children due to an insufficient number of scientific studies confirming its safety in paediatric patients.

The ESPA (European Society for Paediatric Anaesthesiologists) stated, in reference to the above decision of the FDA, that tramadol may be used in children in European countries but only in hospital settings.

Tramadol also induces adverse drug interactions. In the case of postoperative nausea and/or vomiting, the use of ondansetron should be avoided. Moreover, metoclopramide should not be used as an antiemetic during treatment with tramadol because of the risk of seizures. The most common dosages of opioids used in children are presented in Tables 6 and 7.

It should be remembered that the majority of opioids induce immunosuppression, which may

TABLE 6. Dosage of opioids

Opioid	Route of administration	Dose	Interval between doses (hours)	Infusion
Morphine 0–18 years of age	Intravenous, subcutaneous	25–100 μg kg^{-1} b.w.	3–4	10–40 μg kg^{-1} h^{-1}
	Intravenous	20–50 μg kg^{-1} b.w.	4	–
Fentanyl* 0–18 years of age	Intravenous	1–2 μg kg^{-1} b.w.	Single bolus (PRN)	0.5–2 μg kg^{-1} h^{-1}
	TTS	12 μg h^{-1} > 2 years of age	72 hours	
Sufentanil** 0–18 years of age	Intravenous	0.5–1 μg kg^{-1} b.w.	Single bolus (PRN)	0.05–0.15 μg kg^{-1} h^{-1}
Tramadol*** > 1 year of age	Intravenous	1–1.5 mg kg^{-1} b.w. > 1 year of age	4–6 Max. 8 mg kg^{-1} daily Max. 400 mg daily	0.07–0.25 mg kg^{-1} h^{-1}
	Oral	50–100 mg > 12 years of age 1–2 mg kg^{-1} b.w. 1–12 years of age		–
Oxycodone > 12 years of age	Intravenous, oral	0.05–0.15 mg kg^{-1} b.w.	3–4	–
Nalbuphine > 18 months of age	Intravenous	0.1–0.2 mg kg^{-1} b.w.	3–6	Bolus 0.2 mg kg^{-1} b.w. Infusion 0.05–0.1 mg kg^{-1} h^{-1}
Buprenorphine*** > 1 year of age	Sublingual	0.2–0.4 mg > 12 years of age 0.1–0.3 mg from 6 to 12 years of age	6–8	
	Intravenous	0.3–0.6 mg > 12 years 3–6 μg kg^{-1} b.w. (max. 9 μg kg^{-1} b.w.) 1–12 years		
	TTS	35 μg h^{-1}*	96	No studies in children

* To be used in paediatric intensive care units, initially in a bolus and next in a continuous intravenous infusion.

** Effectiveness and safety of sufentanil in children under 2 years of age have been documented in a limited number of cases; nevertheless, it is recommended in general anaesthesia from day 1 of life.

*** See: dosage and route of administration according to age groups.

TTS – transdermal therapeutic system

TABLE 7. Patient-controlled analgesia

Drug	Initial dose	Infusion	Bolus	Max. 4-hour daily dose	Refraction time
Morphine	50–100 μg kg^{-1} b.w.	1–4 μg kg^{-1} h^{-1}	10–20 μg kg^{-1} b.w.	300 μg kg^{-1} b.w.	10–15 min
Fentanyl	0.5–1 μg kg^{-1} b.w.	0.5–1 μg kg^{-1} h^{-1}	0.5–1 μg kg^{-1} b.w.	4–8 μg kg^{-1} b.w.	5–10 min
Oxycodone	0.03 mg kg^{-1} b.w.	No data in children	0.03 mg kg^{-1}	No data in children	5–10 min
Nalbuphine	0.1–0.2 mg kg^{-1} b.w.	0.02 mg kg^{-1} h^{-1}	0.02 mg kg^{-1} b.w.	0.4 mg kg^{-1} b.w.	5 min

result in an increased risk of postoperative infection. Another significant phenomenon that may occur during the use of ultra-short-action opioids (e.g. remifentanil) is the risk of opioid-induced hyperalgesia (opioid paradox), which manifests in increasing pain intensity despite opioid dose escalation [68].

Non-opioid analgesics

Non-opioid analgesics should be used for pain management in children – *recommendation I A*.

Non-opioid analgesics constitute a heterogenous group of drugs which includes paracetamol, metamizole, nonsteroidal anti-inflammatory drugs (NSAIDs, e.g. ibuprofen, naproxen, ketoprofen, diclofenac) and selective cyclooxygenase 2 (COX-2) inhibitors (e.g. celecoxib). They exert analgesic and antipyretic effects; some of them also have anti-inflammatory effects. Their detailed properties and mechanisms of action were specified in the recent guidelines for postoperative pain management of 2018 [69]. They may be used in monotherapy and as part of multimodal analgesia in cases of increased pain intensity. This enables the spectrum of analgesic effects of other analgesic drugs to be broadened and the total dose of opioid analgesics to be reduced. The ceiling doses have been determined for all non-opioid analgesics; above the ceiling dose, the analgesic effect does not increase, while the risk of complications is significantly higher.

PARACETAMOL

Paracetamol is recommended for pain management in children – *recommendation I A*.

Paracetamol (acetaminophen) is the most common non-opioid analgesic used in paediatrics. Its mechanism of action is complex and involves blockade of prostaglandin production in the CNS, activation of the serotonergic descending pathways (5-hydroxytryptamine – 5-HT), antagonistic action in relation to the NMDA (N-methyl-D-aspartate) receptor and substance P in the spinal cord as well as modulation of nitric oxide production. Additionally, it induces analgesia, acting as an agonist of the cannabinoid receptors. Paracetamol effectively relieves mild to moderate pain. It can be administered intravenously, orally or rectally, although some scientific reports have demonstrated diminished or unpredictable bioavailability when administered by rectum [70]. Administered orally at standard doses of 15 mg kg^{-1}, paracetamol is well tolerated, effective and induces few side effects. When the rectal route is used, higher doses are necessary, i.e. 25–40 mg kg^{-1} [71–75]. The pharmacokinetics of paracetamol is body weight-dependent, but it remains relatively stable from the 18th month of life. The most common adverse effect of paracetamol is its hepatotoxicity, which can be prevented by not exceeding the maximum daily dose, which changes with age and maturity of the liver (Table 8). Paracetamol is a significant component of multimodal analgesia, and is often combined with other non-opioid analgesics, e.g. metamizole and NSAIDs. The combined use of paracetamol, NSAIDs plus opioids enables the total postoperative dose of opioids to be reduced significantly [76–84].

METAMIZOLE

Metamizole may be used for pain management in children – *recommendation I B*.

Metamizole is a non-opioid analgesic with analgesic, antipyretic and spasmolytic effects; it also shows synergism of action with NSAIDs, paracetamol and opioids. Metamizole inhibits prostaglandin synthesis, mainly by inhibiting cyclooxygenase 1

TABLE 8. Dosage of paracetamol in neonates, infants and children

Body weight (kg)	Route of administration	Dose (mg kg^{-1} b.w.)	Intervals between doses (hours)	Max. daily dose (mg kg^{-1} b.w.)
< 5 (neonates)	Intravenous	7.5 mg kg^{-1} b.w.	4–6	30 mg kg^{-1} b.w.
	Oral	7.5–10 mg kg^{-1} b.w.	4–6	40 mg kg^{-1} b.w.
	Rectal	15 mg kg^{-1} b.w.	4–6	60 mg kg^{-1} b.w.
5–10	Intravenous	10 mg kg^{-1} b.w.	4–6	40 mg kg^{-1} b.w.
	Oral	10–15 mg kg^{-1} b.w.	4–6	40–60 mg kg^{-1} b.w.
	Rectal	15–20 mg kg^{-1} b.w.	4–6	60–90 mg kg^{-1} b.w.
10–50	Intravenous	15 mg kg^{-1} b.w.	4–6	60 mg kg^{-1} b.w.
	Oral	15 mg kg^{-1} b.w.	4–6	60 mg kg^{-1} b.w.
	Rectal	20–40 mg kg^{-1} b.w.	4–6	80–160 mg kg^{-1} b.w.
> 50	Intravenous	1 g	4–6	4–5 g
	Oral	1 g	4–6	4–5 g

TABLE 9. Dosage of metamizole

Body weight (kg)	Route of administration	Dose	Intervals between doses (h)	Max. daily dose
< 10 (from 3 months)	Intravenous	8–15 mg kg^{-1} b.w.*	6–8	40–60 mg kg^{-1} b.w.
	Oral	8–15 mg kg^{-1} b.w.*	6	40–60 mg kg^{-1} b.w.
10–50	Intravenous	10–15 mg kg^{-1} b.w.	6	60 mg kg^{-1} b.w.
	Oral	10–15 mg kg^{-1} b.w.	6	60 mg kg^{-1} b.w.
> 50	Intravenous	1.0 g	6–8	4.0 g
	Oral	1.0 g	6–8	4.0 g
	Intravenous infusion	2.5 mg kg^{-1} h^{-1}	–	60 mg kg^{-1} b.w.

* The recommended dose – 10 mg kg^{-1} of body weight

(COX-1) and COX-2; moreover, it modulates nociception induced by substance P.

Additionally, it affects the cannabinoid system (analgesic and antipyretic action). Its spasmolytic action results from inhibition of adenosine reuptake in the CNS and its influence on the cannabinoid system [85–89]. Thanks to the relaxing smooth muscle effect, metamizole is particularly useful when pain is accompanied by a spastic component.

It should be remembered that there is a risk of hypotension when the intravenous administration is too fast, especially in patients with hypovolaemia (Table 9).

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs may be used for pain management in children – *recommendation I A*.

Nonsteroidal anti-inflammatory drugs are COX-1 and COX-2 inhibitors which inhibit the production of prostaglandins. They are effective in every type of pain (mechanical, inflammatory, visceral). The analgesic and anti-inflammatory effects of this group of drugs are also accomplished by inhibition of the expression of inducible nitric oxide synthase and of NF-κB activation, activation of the system of lipoxins and inhibition of substance P activity. Additionally, the action of NSAIDs may result from both activation of supraspinal cholinergic pathways and activation of the system of endogenous opiate-similar peptides. Thanks to their use, the opioid demand can be reduced by as much as 50%, thereby reducing the incidence of side effects of opioids. Unfortunately, NSAIDs cause numerous adverse effects. They have to be used with caution in children with allergies or asthma, stomach or duodenal ulcers, liver failure, or kidney failure and in children with risk factors for failure of the above organs, such as dehydration, shock, multiple organ failure or increased risk of bleeding (anti-aggregation effect on platelets by inhibiting COX-1). Moreover, several drugs of the NSAID group should not be combined [90–95]. Dosages of NSAIDs in children are presented in Table 10.

Co-analgesics

in pharmacotherapy of pain, co-analgesics (adjuvant analgesics) are intended to enhance the analgesic effect and supplement the therapy with additional pharmacodynamic mechanisms. Another important application is to treat side effects caused by other groups of drugs used for pain management.

LIDOCAINE

Lidocaine may be used as a co-analgesic for pain management in children – *recommendation I B*.

In anaesthesiology, lidocaine has been used as an anaesthetic and analgesic for over 80 years.

TABLE 10. Dosages of nonsteroidal anti-inflammatory drugs in children

NSAID	Route of administration	Dose	Intervals between doses (hours)	Max. daily dose
Ibuprofen > 3 months	Oral, rectal, intravenous*	5–10 mg kg^{-1} b.w.	6–8	20–30 mg kg^{-1} b.w.
Diclofenac > 1 year	Oral, rectal	0.5–3 mg kg^{-1} b.w.	8	3–9 mg kg^{-1} b.w.
Naproxen > 3 years	Oral, rectal	5–7.5 mg kg^{-1} b.w.	12	10–15 mg kg^{-1} b.w.
Nimesulide > 12 years	Oral	1 mg kg^{-1} b.w.	12	2 mg kg^{-1} b.w.
Ketoprofen > 15 years**	Oral, intravenous	1 mg kg^{-1} b.w.	8	3 mg kg^{-1} b.w.

*For children > 6 years of age and ≥ 20 kg of body weight.

** Dexketoprofen – effectiveness and safety in children has not been established.

Since then, various methods of its administration have been developed. Lidocaine is characterised by several important properties. It lowers pain intensity in the early postoperative period, reduces the incidence of nausea and vomiting, accelerates the restoration of gastrointestinal function, and induces preventive analgesia; moreover, it has anti-inflammatory and immunomodulatory effects. Its use in the perioperative period as a component of multimodal analgesia enables the reduction of opioid doses [96]. Unfortunately, the effects of lidocaine in paediatric patients have not yet been thoroughly studied [97–100].

An intravenous lidocaine infusion is mainly indicated prior to open or laparoscopic abdominal surgical procedures. Lidocaine has a beneficial effect in patients after thoracic surgery and multi-level spinal surgery. It can be administered intravenously in pre-emptive analgesia as a bolus at a dose of 1.5 mg kg^{-1} (dose range 1–3 mg kg^{-1}) or during the induction of anaesthesia; subsequently its use should be continued in an infusion at a dose of 1.5–3.0 mg kg^{-1} h^{-1}. Doses should be calculated based on ideal body weight, which is particularly important in obese children. The infusion can be terminated at the completion of surgery or continued for 24 hours. Special care should be taken when lidocaine is used in patients with liver and kidney dysfunction due to possible accumulation of its active metabolites. It is worth noting that lidocaine is not removed during dialysis. It should be used only in children with stable haemodynamic parameters. If the symptoms of local anaesthetic systemic toxicity (LAST) are observed, an intravenous lipid emulsion should be immediately administered according to the current recommendations. Management in LAST is described in the section below devoted to regional anaesthesia techniques.

GABAPENTINOIDS

Gabapentinoids may be considered as co-analgesics for pain management in children – *recommendation II C*.

Gabapentin and pregabalin are used to treat chronic neuropathic pain in children and adolescents; it should be emphasised, however, that their use is off-label.

The above drugs have found their place in multimodal analgesia in the perioperative period as an element of premedication [101]. They inhibit hyperalgesia as well as allodynia and exert only a slight effect on nociception.

Perioperative use of gabapentin and pregabalin improves the quality of analgesia at rest and on movement and reduces opioid requirements in the postoperative period [102, 103]. Gabapentin and pregabalin decrease the incidence of opioid-induced adverse effects, particularly nausea, vomiting and urine retention. In children above 12 years of age, an oral dose of 300 mg of gabapentin may be administered 1–2 hours before the planned anaesthesia, whereas in younger children the recommended dose is 10 mg kg^{-1}. To date, the safety of pregabalin in children and adolescents under 17 years of age has not been demonstrated, and the suggested doses may be based only on the doses for adults, in whom the usual oral dose is 150–300 mg. The available literature data are very cautious about potential benefits of using gabapentinoids for pain management in children [104].

ALPHA-2 ADRENERGIC RECEPTOR AGONISTS

Alpha-2 adrenergic receptor agonists may be used as co-analgesics for pain management in children – *recommendation I A*.

Alpha-2 adrenomimetic drugs are widely used in the perioperative multimodal management of pain [105–112]. They act by stimulating α-2 receptors in the posterior horn of the spinal cord and supraspinally at the locus coeruleus (they inhibit glutamate and substance P release). Perioperative use of α2-adrenergic receptor agonists, clonidine or dexmedetomidine, lowers the intensity of pain in the postoperative period, allows opioid doses to be decreased and reduces the incidence of nausea. The above drugs are most often used in premedication (orally, intravenously or nasally) and intraoperatively (intravenously); their supply may be continued in the postoperative period (repeated doses or continuous infusions). The most common side effects limiting the use of α2-adrenergic receptor agonists include hypotension, bradycardia and excessive sedation. The suggested doses of dexmedetomidine during general anaesthesia range from 0.3 to 1 μg kg^{-1} in a single bolus administered during induction or at the end of the procedure, or in a continuous infusion at a dose of 0.3 to 0.7 μg kg^{-1} h^{-1} (0.5 on average).

KETAMINE

Ketamine may be used as a co-analgesic for pain management in children – *recommendation I A*.

Ketamine exhibits a multidirectional mechanism of action. It inhibits activation of the NMDA receptor, induces analgesia and prevents the development of persistent postoperative pain. By activating the adrenergic neurons and inhibiting synaptic monoamine reuptake in the sympathetic system, ketamine provides haemodynamic stability of patients

suffering from perioperative or traumatic shock. Ketamine is characterized by a lack of inhibitory effects on the respiratory centre. It dilates the bronchioles, does not inhibit upper airway reflexes, and blocks the activation of proinflammatory cytokines. In the perioperative period, subanaesthetic doses of ketamine are recommended; they provide haemodynamic stability as well as effective analgesia, and prevent psychomimetic symptoms [113–122]. Ketamine doses during general anaesthesia range from 0.1 to 0.3 mg kg^{-1} in a single bolus administered during induction and repeated every 30–60 minutes or in a continuous infusion at a dose of 0.06 to 0.12 mg kg^{-1} h^{-1} administered not longer than 24 hours. When intravenous infusions are used, continuous monitoring of patients' haemodynamic parameters is required.

CORTICOSTEROIDS

Corticosteroids may be used for pain management in children – *recommendation I B*.

Inflammation plays a significant role in the development of postoperative pain. Limitation of inflammation may decrease the pain experienced by patients. Anti-inflammatory effects of corticosteroids involve inhibition of the formation and release of proinflammatory cytokines. Corticosteroids stabilize the cell membranes of neurons in the peripheral tissues and exert an antinociceptive effect at the spinal level.

Dexamethasone is an adjuvant most frequently used to treat pain in children, especially after head and neck surgery as well as in procedures lasting over 1 hour. Dexamethasone at a dose of 0.1–0.5 mg kg^{-1} decreases pain intensity and opioid requirements in the postoperative period; moreover, it prevents postoperative nausea and vomiting [123–127].

A single dose of dexamethasone has not been demonstrated to increase the incidence of infections or to delay postoperative wound healing.

MAGNESIUM SULPHATE

Magnesium sulphate may be considered as a co-analgesic for pain management in children – *recommendation II C*.

Magnesium is an antagonist of NMDA receptors located in the peripheral and central nervous system; the highest concentration of these receptors is found in the anterior horns of the spinal cord. NMDA receptors are associated with the development of central sensitization. Their stimulation intensifies nociceptive impulsation clinically, manifesting as hyperalgesia and allodynia. By decreasing the concentration of interleukin 6 (IL-6) and tumour necrosis factor α (TNF-α), magnesium ions also exert anti-inflammatory effects [128–130]. Intravenous doses of magnesium sulphate during general anaesthesia are a 30–50 mg kg^{-1} bolus, followed by an infusion of 15 mg kg^{-1} h^{-1}.

It should be remembered that magnesium ions may delay the restoration of neuromuscular conduction and cause bradycardia.

The available research data are insufficient to assess the effectiveness of magnesium sulphate administered to reduce postoperative pain and opioid requirements in paediatric patients.

REGIONAL ANALGESIA IN CHILDREN

Regional anaesthesia techniques should be used during pain management in children – *recommendation I A*.

Regional anaesthesia is one of the fundamental elements of modern pain management in children. It provides significantly superior and longer pain control in comparison with systemic analgesia; moreover, it allows opioid analgesic requirements to be reduced. In children, unlike in adults, regional blocks should be performed in deep sedation or under general anaesthesia. The use of ultrasound imaging or a nerve stimulator is an important element that improves the quality and effectiveness of this type of analgesia.

Since 2012, the ESRA (European Society of Regional Anaesthesia and Pain Therapy) and ASRA (American Society of Regional Anesthesia and Pain Medicine) experts have paid attention to the issues of conduction anaesthesia in children. Their joint discussions focus on the safety of regional analgesia during general anaesthesia or in deep sedation in paediatric patients, the use of a test dose, the risk of acute compartment syndrome, dosage of local anaesthetics as well as the use of co-analgesics [131–133]. The total risk of complications of regional anaesthesia is low and is estimated at 0.66%, whereas the risk of nerve damage almost equals 0%. Rare neurological complications of regional anaesthesia in children may be masked by general anaesthesia [134].

Test dose

To detect an incidental administration of a local anaesthetic (LA) to an artery or a vein during a conduction block, an adrenaline test dose (0.25 μg kg^{-1} body weight [b.w.]) is recommended, which can be administered to children. In young children, however, the usefulness of the above method is limited because of the initially higher heart rate [135]. It is essential, though, that each dose of LA is administered slowly, in fractionated doses of 0.1–0.2 mL kg^{-1} body weight, and the electrocardiogram is continuously monitored (*recommendation I B*).

Acute compartment syndrome

One of the possible complications of regional anaesthesia is acute compartment syndrome (ACS), which develops with time due to increased pressure within a closed anatomical compartment of the limb. It impairs blood circulation, innervation and muscle function. Left untreated, ACS leads to ischaemia, and eventually to necrosis, muscle contractures and fibrosis as well as to irreversible impairment of the activity of the affected part of the limb. In children, diagnosis of ACS may be difficult. The main symptom of ACS is excruciating pain which is not associated with the underlying disease. The pain is usually resistant to opioids. It is worth noting that conduction anaesthesia may delay the diagnosis of acute limb ischaemia by masking the occurrence of pain connected with this disease. However, ischaemic pain and nociceptive pain are transmitted through various nerve fibres. Therefore, acute pain experienced by the patient receiving continuous conduction anaesthesia is a pathognomonic symptom of ACS.

At present, there is no evidence confirming that the use of conduction anaesthesia in children increases the risk of ACS or delays its diagnosis. Low concentrations of LA in single doses or in a continuous infusion, i.e. 0.1–0.25% of bupivacaine or 0.2% of ropivacaine, reduce the risk of ACS [136–140].

Pharmacokinetics of local anaesthetics in children

In the group of neonates, the level of plasma α1-acid glycoprotein is decreased, which causes a high plasma concentration of the free LA fraction, thereby increasing the risk of toxic effects. Correct concentrations of the above protein are usually observed after the first year of life. In infants aged less than 6 months, whose liver clearance and metabolism are half of those in adults, LA elimination half-time is prolonged. Another factor likely to contribute to LA accumulation is the higher volume of distribution. Therefore, the flow of the basic LA during continuous blocks should be reduced by half. Moreover, incomplete myelinization of the nerve fibres in children up to 1 year of age makes them more sensitive to LA effects.

Toxic effects of local anaesthetics in children

The toxic complication of LAs is LAST, particularly after the administration of bupivacaine. Since the majority of regional blocks are performed in paediatric patients under general anaesthesia or in deep sedation, the first observed symptoms of LAST will be associated with the cardiovascular system (cardiotoxicity) and not with the CNS. The risk of LAST in infants and children is low; additionally, increasingly common use of ropivacaine or levobupivacaine, which have a more beneficial therapeutic profile than bupivacaine, decreases the incidence of LAST. Adherence to LA dosage recommendations is of the utmost importance. In cases of LA overdose and development of LAST symptoms, a 20% lipid solution at a dose of 1.5 mL kg^{-1} (0.3 g kg^{-1}) should be administered within one minute and followed by its continuous infusion at a dose of 0.24 mL kg^{-1} min^{-1} (0.05 g kg^{-1} min^{-1}); cardio-pulmonary resuscitation (CPR) should be continued. If circulatory stability is not achieved, the bolus should be repeated up to the maximum dose of 3 mL kg^{-1} every 3–5 minutes until the total dose of 10 mL kg^{-1} is reached. Intravenous infusions should be continued until circulatory stability is restored [141–148]. Midazolam is recommended in cases of seizures, whereas amiodaron is recommended as an antiarrhythmic drug.

Peripheral nerve blocks

In the paediatric population, techniques of regional anaesthesia are the same as those used in adults. The standard which improves the quality and safety of block analgesia in children, as well as in adults, is the use of ultrasound techniques and peripheral nerve stimulators [149–151]. It should be noted that the anatomical structures in children (vessels, nerves) are significantly smaller and are localised shallowly; thus, the use of high-frequency transducers is necessary.

The smaller the patient is, the larger is the disproportion between the size of the transducer front and the patient.

The transducers intended for paediatric patients are characterized by a shorter ultrasonic beam; therefore guiding the needle in the axis of the transducer is much more difficult. Moreover, the equipment should be adjusted to paediatric patients and the needle should be of appropriate length and diameter. Of note, individual nerve structures in children are characterized by much lower echogenicity as compared to adults. The smaller the patient is, the larger are the differences and the more difficult is the visualisation of a given structure.

Contrary to nerves, the fascial structures and aponeuroses in children show significantly higher echogenicity. Thus, compartment blocks, e.g. fascial iliac block, transversus abdominis plane (TAP) block or rectus sheath block (RSB), are much easier to perform. Looser connections within fascial compartments in children promote better spread/distribution of LA and wider ranges of blocks. Dosages of drugs most frequently used in peripheral blocks in children are presented in Tables 11 and 12.

Furthermore, it should be remembered that arterial and venous pressures are lower in paediatric patients; therefore, the blood vessels, the main

TABLE 11. Recommended doses of local anaesthetics for most common ultrasound-guided peripheral blocks in children

Block	0.25% Bupivacaine/ levobupivacaine 0.2% Ropivacaine
Brachial plexus (interscalene)	0.1–0.2 mL kg^{-1} b.w.
Brachial plexus (supraclavicular)	0.2–0.5 mL kg^{-1} b.w.
Brachial plexus (infraclavicular)	0.2–0.5 mL kg^{-1} b.w.
Brachial plexus (axillary)	0.1–0.2 mL kg^{-1} b.w.
Femoral nerve	0.2–0.4 mL kg^{-1} b.w.
Sciatic nerve	0.2–0.4 mL kg^{-1} b.w.
Saphenous nerve	0.2–0.4 mL kg^{-1} b.w.
Transverse abdominis plane block	0.2–0.3 mL kg^{-1} b.w. (per side)
Iliohypogastric nerve Ilioinguinal nerve	0.075–0.1–0.4 mL kg^{-1} b.w.
Rectus sheath block	0.1–0.2 mL kg^{-1} b.w.
Back extensor plane block	0.2–0.5 mL kg^{-1} b.w.
Compartment blocks within the thoracic wall	0.2 mL kg^{-1} b.w.
Serratus anterior plane block	0.4 mL kg^{-1} b.w.
Quadratus lumborum block	0.2 mL kg^{-1} b.w.
Penile block	0.1 mL kg^{-1} b.w. (per side)

TABLE 12. Recommended doses of local anaesthetics administered in continuous infusions in peripheral blocks in children

Block – continuous infusion	0.125% Bupivacaine/levobupivacaine 0.2% Ropivacaine (in neonates and infants dose reduction by 50% on day 2)
Femoral nerve	0.1–0.3 mL kg^{-1} h^{-1}
Sciatic nerve	0.1–0.3 mL kg^{-1} h^{-1}

landmarks in peripheral blocks, are more susceptible to the transducer's pressure and may be totally constricted during ultrasound examinations, which impairs the sonoanatomical image and makes the identification of nerve structures more difficult. Furthermore, it should be borne in mind that the younger the patient is, the shorter is the time for performing the block and the shorter is its duration.

Central blocks

As in adults, epidural and spinal blocks are performed in children. The most common epidural block performed in small children is the caudal block, followed by the lumbar block and the thoracic block. The spinal cord in children terminates most frequently at the L2 level; in neonates, it terminates at the level of L3/L4 (in adults at the level of L1). In children, the dural sac extends to the S3 level (in adults the S1 level) (Tables 13 and 14). Due to the above conditions, the risk of neurological complications associated with an unintentional nerve puncture (particularly when the procedure is performed under general anaesthesia) and of intrathecal anaesthetic administration during sacral anaesthesia is relatively high.

In children, deep hypotension after central blocks is rarer than in adults, which is associated with the immaturity of the sympathetic nervous system and lower vascular volume within the lower limbs.

Both isobaric and hyperbaric LA solutions may be used in central subarachnoid blocks in children. The actual duration of the block is shorter in infants than in adults, which is related to the increased volume of the cerebrospinal fluid in infants. Dosages of LAs most frequently used in children are presented in Tables 15–17.

Co-analgesics in regional anaesthesia

Agonists of α2-receptors may be used as co-analgesics during regional anaesthesia in children – *recommendation II C*.

In order to prolong the block duration in children, a combination of LAs and co-analgesics, such as agonists of α2-receptors (clonidine, dexmedetomidine), may be applied. The choice of the above drugs is justified by the fact that they probably do not exert a neurotoxic effect involving intensification of apoptosis of spinal cord neurons in humans [152–156].

The most likely mechanism of action of α2-agonists in regional blocks involves inhibition of the hyperpolarisation-activated cationic currents (I_h), most strongly marked in the C fibres conducting pain, and slightly less pronounced in A motor fibres.

The use of clonidine or dexmedetomidine in epidural blocks, compartment blocks and peripheral nerve blocks improves the quality and duration of analgesia, as compared to the use of LAs alone, thereby reducing their doses by as much as 25–50%. Moreover, the administration of such adjuvants prolongs the action of the first analgesic dose from 14 to 22 hours [157].

TABLE 13. Anatomical differences between children and adults

Age	The level of termination of the spinal cord	The level of termination of the dural sac	Interspine line	Volume of CSF	CSF volume (%) in the spinal canal
Neonate	L3	S3–S4	L5–S1	10 mL kg^{-1} b.w.	Not known?
Infant	L2	S2	L4–L5	4 mL kg^{-1} b.w.	50
Adult	L1	S2	L3–L4	2 mL kg^{-1} b.w.	25

CSF – cerebrospinal fluid

Adding adjuvants seems to be relatively safe and beneficial for patients, especially regarding lower risk of nausea, vomiting or urination disorders, while maintaining the effective potency [155]. However, when α2-agonists are administered, the risk of bradycardia and hypotension should be considered, particularly when the doses are higher and exceed 1–2 μg kg^{-1}. Special care should be exercised in neonates and infants whose clearance of the above drugs is 1/3 of the adult value [156]. Neonates, premature and born at full term, undergoing subarachnoid blocks with clonidine, are likely to develop (within the first 24 h) transient excessive sedation accompanied by bradycardia and apnoea, which commonly resolves spontaneously and without incidents of desaturation [158]. In other children, slight or moderate sedation may occur after 1–3 hours following the block, which can be regarded as a quite beneficial effect improving the emotional and mental state of the child.

Dexmedetomidine, a more selective agonist compared to clonidine, shows action similar to clonidine at equipotential doses, yet the block induced by it, both sensory and motor, is more potent [156].Ketamine, quite recently used as a co-analgesic in central blocks, is not currently recommended because of the potential risk of damage to the neurons within the spinal cord [151, 159] (*recommendation I A*).

TABLE 14. Sizes of Tuohy epidural needles and epidural catheters in children

Body weight (kg)	Size (G)	Catheter (G)
< 5	20	24
5–20	19	23
> 20	18	20

SPECIFIC CLINICAL SITUATIONS

Acute post-traumatic pain

Acute post-traumatic pain dominates in the first 72 hours after trauma. This mixed pain is caused by direct and prolonged nociceptive stimulation originating from the damaged tissues. Trauma causes the release of inflammatory response mediators in the tissues accompanied by sensitisation of the CNS structures, leading to the development of an inflammatory and neuropathic component of pain. Proper assessment of pain intensity is essential for effective pain management (Tables 3 and 4).

Relief of acute post-traumatic pain

Attending to a child at the scene of an accident and during transport

Pain intensity above 7 points according to the VAS/NRS/FLACC requires the administration of a strong opioid, e.g. fentanyl or morphine (Table 6). Fentanyl allows a prompt analgesic effect to be

TABLE 15. Dosages of local anaesthetics in children

	Bupivacaine	Levobupivacaine	Ropivacaine	Lidocaine	Prilocaine
Onset of action	10–15 min	10–15 min	10–15 min	5–10 min	5–10 min
Maximum dose (without adrenaline)	2.5 mg kg^{-1} b.w.	2.5 mg kg^{-1} b.w.	2 mg kg^{-1} b.w.	4 mg kg^{-1} b.w.	6 mg kg^{-1} b.w.
Maximum dose (with adrenaline)	2.5 mg kg^{-1} b.w.	2.5 mg kg^{-1} b.w.	Not used	7 mg kg^{-1} b.w.	8 mg kg^{-1} b.w.
Duration of action (without adrenaline)	3–12 h	3–12 h	3–12 h	1–2 h	1–2 h
Duration of action (with adrenaline)	4–12 h	4–12 h	No data	2–4 h	2–4 h

TABLE 16. Dosages of drugs for epidural anaesthesia in children

Age	Bupivacaine	Ropivacaine	Clonidine	Fentanyl	Sufentanil
Single injection of local anaesthetic*					
< 1 year of age	0.25%; 1 mL kg^{-1} b.w.	0.2%; 1.2 mL kg^{-1} b.w.	1–1.5 μg kg^{-1} b.w.	2 μg kg^{-1} b.w.	0.2 μg kg^{-1} b.w.
> 1 year of age	0.25%; 1 mL kg^{-1} b.w., max. 20 mL	0.2–0.5%; 3.5 mg kg^{-1} b.w., max. 20 mL	1–1.5 μg kg^{-1} b.w.	2 μg kg^{-1} b.w.	0.2 μg kg^{-1} b.w.
Continuous infusion of local anaesthetic*					
< 3 months of age	0.0625–0.125%; 0.2 mg kg^{-1} h^{-1}	0.1–0.2%; 0.2 mg kg^{-1} h^{-1}	0.12–0.2 μg kg^{-1} h^{-1}	1–2 μg kg^{-1} b.w.	0.1–0.2 μg kg^{-1} b.w.
3 months – 1 year of age	0.125%; 0.3 mg kg^{-1} h^{-1}	0.1–0.2%; 0.3 mg kg^{-1} h^{-1}	0.12–0.2 μg kg^{-1} h^{-1}	1–2 μg kg^{-1} b.w.	0.1–0.2 μg kg^{-1} b.w.
> 1 year of age	0.125%; 0.3–0.4 mg kg^{-1} h^{-1}	0.1–0.2%; 0.4 mg kg^{-1} h^{-1}	0.12–0.2 μg kg^{-1} h^{-1}	1–2 μg kg^{-1} b.w.	0.1–0.2 μg kg^{-1} b.w.

*Test dose of adrenaline – 0.25 μg kg^{-1} b.w.

TABLE 17. Dosages of local anaesthetics for subarachnoid anaesthesia in children

Age	0.5% Bupivacaine/ levobupivacaine (mg kg^{-1} b.w.)	0.5% Ropivacaine (mg kg^{-1} b.w.)
Neonates/infants	0.5–1.0	0.5–1.0
1–7 years of age*	0.3–0.5	0.5
> 7 years of age*	0.2–0.3	0.3–0.4
Block duration (min)	30–180 (80)	34–210 (96)

*With morphine (approved for subarachnoid administration) at a dose of 5–15 μg kg^{-1}, fentanyl 0.2–2 μg kg^{-1} or clonidine 1–2 μg kg^{-1})

achieved, and its action is short. However, it should be remembered that fentanyl generates muscle rigidity, particularly in the thoracic wall and the glottis, which increases the risk of respiratory failure in non-intubated children.

Ketamine is another effective analgesic. There are various routes of its administration – intravenous, intramuscular or nasal using a special applicator. By inhibiting the activation of the NMDA receptor, ketamine induces effective analgesia and prevents the development of persistent post-traumatic pain. Additionally, it activates the sympathetic nervous system, ensuring haemodynamic stability immediately after trauma, dilates the bronchioles and does not inhibit upper airway reflexes.

When the intensity of pain is 1–6 points according to the VAS/NRS/FLACC scale, non-opioid analgesics and nonsteroidal anti-inflammatory drugs are effective (Tables 8–10).

Instantly after trauma, analgesics should be administered intravenously or via the intramedullary route, since at that time the blood flow in the muscles and subcutaneous tissue is quickly impaired.

Management of hospitalized children – provision of care in the accident and emergency department or in the hospital ward

In such situations, pain management is based on the same principles and involves the use of similar drugs and methods as those used to relieve other types of acute pain, e.g. postoperative (see the section concerning fundamental principles of pain management in children as well as algorithms).

In cases of pain intensity ranging from 1 to 6 points according to the VAS/NRS/FLACC scale, a combination of non-opioid analgesics, i.e. paracetamol and metamizole, and one NSAID should be used. Such a combination therapy induces effective analgesia and helps to reduce local inflammation and tissue oedema due to the anti-inflammatory effects of the NSAID.

If no analgesic effect has been obtained, a weak opioid, e.g. nalbuphine, should be included or ketamine should be administered. When pain intensity is 7 points or more according to the VAS/NRS/FLACC scale, multimodal analgesia combined with the techniques of conduction analgesia is optimal.

Burn pain

Distinguishing different phases of burn disease is essential for effective analgesia. In the early hypodynamic phase (up to 48 hours), the elimination of drugs by the liver and kidneys is diminished due to reduced cardiac output and increased systemic and pulmonary vascular resistance. Furthermore, massive loss of plasma and albumins, increased concentration of α1-acid glycoprotein and aggressive fluid resuscitation result in an increase in the volume of distribution and alter the pharmacokinetics of analgesics, especially hydrophilic ones.

In the hyperdynamic phase (48 hours after trauma and more), however, the cardiac output significantly increases; the renal and hepatic flow and drug clearance also increase.

Demand for morphine (a hydrophilic drug) increases in both the hypodynamic (an increase in distribution space, loss of drug with transudate) and hyperdynamic phase (an increase in hepatic and renal flow, lower sensitivity threshold of the opioid μ receptor).

Demand for fentanyl (a lipophilic drug) substantially increases in the hyperdynamic phase (an increase in the hepatic and renal flow, lower sensitivity threshold of the opioid μ receptor).

Demand for ketamine and propofol (lipophilic drugs) significantly increases in the hyperdynamic phase (an increase in the hepatic and renal flow, an increase in the sensitivity threshold of the NMDA receptor). It should be remembered that the use of ketamine in children with burns may cause hypotension resulting from direct effects on the cardiac muscle due to long persistence of high concentrations of catecholamines caused by desensitization and a decreased sensitivity threshold of β-adrenergic receptors.

In children with burns, during changes of dressings or painful diagnostic and therapeutic procedures, a combination of propofol and ketamine (ketofol) may be used.

Demand for lidocaine (a hydrophilic drug) markedly increases because of increased distribution space and increased serum concentration of α1-acid glycoprotein that binds lidocaine.

When opioids are used in children with burns, the opioid paradox should be considered (chronic administration of high doses of opioids may paradoxically intensify pain sensations).

OFF-LABEL USE OF DRUGS IN CHILDREN

Pain management in the paediatric population, as well as the entire pharmacokinetics, faces some

difficulties associated with limited information included in the summary of product characteristics (SPCs) concerning mainly age. It is estimated that over 75% of registered drugs do not have records for children younger than 2 years; for neonates the percentage is as high as 90%. Legal safety of the use of analgesics and co-analgesics, administered systematically or locally, is connected with marketing authorization of a given medicinal substance with specified indications or the absence of authorization, which is reflected in the information included in SPCs [160]. In cases of off-label use of drugs, their prescription should be based on the analysis of other regulations/provisions of law, e.g. Article 6(1). According to the Patient Rights Act, patients have the right to health benefits corresponding to the requirements of current medical knowledge and based on the principle of evidence-based medicine (EBM), which is guided by the overarching idea *Salus aegroti suprema lex est* (The well-being of the patient is the supreme law) [161–163]. The above principles constitute foundations of medical law and medical ethics providing a premise for a state of higher necessity, which is a subsidiary principle [161]. As regards off-label drugs registered and authorized for pain management, if they are used outside the scope specified in SPCs, it should be ascertained that the treatment has been tested in medical practice. Thus, treatment with the use of off-label medications, supported by recommendations or guidelines of scientific societies, should be considered treatment within the scope of current medical knowledge and therefore has the features of an "ordinary" medical procedure [164].

SUMMARY

Management of postoperative pain in children is a practical implementation of the patient's right to relief of suffering.

At the same time, it is a fundamental obligation of physicians responsible for perioperative care of children. The current model is based on the concept of multimodal analgesia, with particular emphasis on techniques of regional anaesthesia which safety is determined by the ability to use ultrasound imaging. Knowledge of pharmacokinetics and pharmacodynamics of analgesics in particular age groups, good organization of the monitoring system, treatment of pain and control of its quality are prerequisites of effective and safe acute pain relief in children.

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ALGORITHM 1. Relief of pain after surgical procedures with minor tissue damage

PRE-OPERATIVE ANALGESIA

Pharmacotherapy to induce the effects of pre-emptive analgesia

- Non-opioid analgesics, e.g.
  - PARACETAMOL 7.5–15 mg kg^{-1} b.w. *i.v.* (dosage according to Table 8)
  - and/or METAMIZOLE 15 mg kg^{-1} b.w. *i.v.* (dosage according to Table 9)
- In combination with NSAID (after exclusion of contraindications, including increased risk of intraoperative NSAID-associated bleeding), e.g.
  - IBUPROFEN 10 mg kg^{-1} b.w. *p.o.* (dosage according to Table 10)

Regional analgesia to induce the effects of pre-emptive analgesia performed under deep analgosedation or general anaesthesia

- Injecting the line of incision with LA (dosage according to Table 15)
- Ultrasound-guided blocks: peripheral nerves, plexuses or nerves of the upper or lower limb (dosage according to Table 11)

POSTOPERATIVE ANALGESIA

Pharmacotherapy – monotherapy or combination therapy administered intravenously or orally

- Non-opioid analgesics, e.g.
  - PARACETAMOL 7.5–15 mg kg^{-1} b.w. *i.v./p.o.* (dosage according to Table 8)
  - and/or METAMIZOLE 15 mg kg^{-1} b.w. *i.v./p.o.* (dosage according to Table 9)
- In combination with NSAID e.g.:
  - IBUPROFEN 10 mg kg^{-1} b.w. *p.o.* (dosage according to Table 10)

If pain intensity is ≥ 4 in the NRS scale despite combination therapy consisting of non-opioid analgesics, an opioid should be administered intravenously (e.g. nalbuphine or morphine) (dosage according to Table 6)

Regional analgesia

- Another injection of the wound with LA (dosage according to Table 15)

In cases of postoperative nausea and/or vomiting, the following should be administered:

- ondansetron 0.1 mg kg^{-1} b.w. *i.v.* (max. 4 mg)
- and/or dexamethasone 0.1–0.2 mg kg^{-1} b.w. *i.v.*
- or metoclopramide 0.1–0.15 mg kg^{-1} b.w. *i.v.*

ALGORITHM 2. Management of pain after surgical procedures with average tissue damage

PRE-OPERATIVE ANALGESIA

Pharmacotherapy to induce the effects of pre-emptive analgesia

- Non-opioid analgesics, e.g.
  - PARACETAMOL 7.5–15 mg kg^{-1} b.w. *i.v.* (dosage according to Table 8)
  - and/or METAMIZOLE 15 mg kg^{-1} b.w. *i.v.* (dosage according to Table 9)
- In combination with NSAID (after exclusion of contraindications, including the increased risk of NSAID-related intraoperative bleeding), e.g.
  - IBUPROFEN 10 mg kg^{-1} b.w. *p.o.* (dosage according to Table 10)

Regional analgesia to induce the effects of pre-emptive analgesia performed under deep analgosedation or general anaesthesia

- Injecting the line of incision with LA (dosage according to Table 15)
- Ultrasound-guided blocks: peripheral nerves, interfascial compartments in thoracic surgery, plexuses or nerves of the upper or lower limb (dosage according to Table 11)

SURGERY

During induction of anaesthesia, the use of co-analgesics should be considered

- LIDOCAINE 1–1.5 mg kg^{-1} b.w. *i.v.* (should not be administered if one of regional analgesia techniques was used)
- DEXAMETHASONE 0.1–0.2 mg kg^{-1} b.w. *i.v.*
- and/or KETAMINE 0.1–0.3 mg kg^{-1} b.w. *i.v.*

Continuation of co-analgesic supply in conduction anaesthesia in the form of intravenous infusions

- LIDOCAINE 1–1.5 mg kg^{-1} h^{-1} b.w. *i.v.* (should not be administered if one of regional analgesia techniques was used)
- KETAMINE 0.06–0.12 mg kg^{-1} h^{-1} b.w. *i.v.*

POSTOPERATIVE ANALGESIA

Pharmacotherapy – combination therapy administered intravenously or orally

- Non-opioid analgesics, e.g.
  - PARACETAMOL 7.5–15 mg kg^{-1} *i.v.* (dosage according to Table 8)
  - and/or METAMIZOLE 15 mg kg^{-1} *i.v.* (dosage according to Table 9)
- In combination with NSAID (dosage according to Table 10)
- Continuation of co-analgesics should be considered:
  - LIDOCAINE 1–1.5 mg kg^{-1} b.w. in *i.v.* infusion (max. 24 h) (**should not be administered if one of the regional analgesia techniques was used**)
  - DEXMEDETOMIDINE 0.3–0.7 μg kg^{-1} b.w. h^{-1} in *i.v.* infusion

If pain intensity is > 4 according to the NRS scale despite combination therapy consisting of non-opioid analgesics and co-analgesics, an opioid should be administered intravenously (e.g. nalbuphine, morphine or oxycodone) (dosage according to Table 6).

- Optionally, an opioid may be administered intravenously using PCA (dosage according to Table 7).

Regional analgesia

- Aother injection of the wound with LA (dosage according to Table 15)
- or, in selected cases, a continuous infusion with LA using an automatic syringe or elastomeric pump through an implanted catheter in the area of peripheral nerves, nerve plexuses, to interfascial spaces or to the postoperative wound (Tables 11, 12 and 15)

In cases of postoperative nausea and/or vomiting, the following should be administered:

- ondansetron 0.1 mg kg^{-1} *i.v.* (max. 4 mg)
- and/or dexamethasone 0.1–0.2 mg kg^{-1} *i.v.*
- or metoclopramide 0.1–0.15 mg kg^{-1} *i.v.*

ALGORITHM 3. Pain management after surgical procedures with significant and extensive tissue trauma

PRE-OPERATIVE ANALGESIA

Pharmacotherapy to induce the effects of pre-emptive analgesia

- Non-opioid analgesics, e.g.
  - PARACETAMOL 7.5–15 mg kg^{-1} b.w. *i.v.* (dosage according to Table 8)
  - and/or METAMIZOLE 15 mg kg^{-1} b.w. *i.v.* (dosage according to Table 9)
- In combination with NSAID (after exclusion of contraindications, including the risk of increased NSAID-related intraoperative bleeding), e.g.
  - IBUPROFEN 10 mg kg^{-1} b.w. *p.o.* (dosage according to Table 10)
- and/or GABAPENTIN in children under 12 years of age 10 mg kg^{-1} b.w., over 12 years of age – 300 mg *p.o.*, PREGABALIN in patients over 17 years of age – 150–300 mg *p.o.*

Regional analgesia to induce the effects of pre-emptive analgesia under deep analgosedation or general anaesthesia

- Continuous epidural analgesia (dosage according to Table 16)
- Thoracic paravertebral block (dosage according to Tables 15, 16)
- Ultrasound-guided blocks: peripheral nerves, interfascial compartments in thoracic surgery, plexuses or nerves of the upper or lower limb (dosage according to Table 11)

SURGERY

During induction of anaesthesia, the use of co-analgesics should be considered

- LIDOCAINE 1–1.5 mg kg^{-1} b.w. *i.v.* (should not be administered if one of the regional analgesia techniques was used)
- DEXAMETHASONE 0.1–0.2 mg kg^{-1} b.w. *i.v.*
- and/or KETAMINE 0.1–0.3 mg kg^{-1} b.w. *i.v.*
- and/or DEXMEDETOMIDINE 0.3–1 μg kg–1 in *i.v.* infusion

Continuation of co-analgesics supply in conduction anaesthesia in the form of intravenous infusions

- LIDOCAINE 1–1.5 mg kg^{-1} h^{-1} b.w. *i.v.* (**should not be administered if one of the regional analgesia technique was used**)
- KETAMINE 0.06–0.12 mg kg^{-1} h^{-1} b.w. *i.v.*
- DEXMEDETOMIDINE 0.3–0.7 μg kg^{-1} h^{-1} b.w. *i.v.*

POSTOPERATIVE ANALGESIA

Pharmacotherapy – intravenous combination therapy

- a strong opioid administered intravenously using PCA or NCA or in continuous intravenous infusions (dosage according to Tables 6, 7)
- non-opioid analgesics, e.g.
  - PARACETAMOL 7.5–15 mg kg^{-1} *i.v.* (dosage according to Table 8)
  - and/or METAMIZOLE 15 mg kg^{-1} *i.v.* (dosage according to Table 9)
- in combination with NSAID (dosage according to Table 10)
- continuation of co-analgesics supply should be considered:
  - LIDOCAINE 1–1.5 mg kg^{-1} b.w. in intravenous infusion (max. 24 h) (***should not be administered if one of the regional analgesia techniques was used***)
  - KETAMINE 0.06–0.12 mg kg^{-1} b.w. *i.v.* (max. 24 h)
  - DEXMEDETOMIDINE 0.3–0.7 μg kg^{-1} h^{-1} in intravenous infusion

In the case of breakthrough pain, additional doses of opioids should be administered intravenously (morphine or oxycodone) (dosage according to Table 6)

Regional analgesia is a continuation of intraoperative anaesthesia

- continuous epidural infusion of LA with opioid (dosage according to Table 16)
- or continuous infusion of LA using an automatic syringe or elastomeric pump through the implanted catheter in the area of peripheral nerves, nerve plexuses, to interfascial spaces or to the postoperative wound (Tables 11, 12 and 15)

In the case of postoperative nausea and/or vomiting, the following should be administered:

- ondansetron 0.1 mg kg^{-1} *i.v.* (max. 4 mg)
- and/or dexamethasone 0.1–0.2 mg kg^{-1} *i.v.*
- or metoclopramide 0.1–0.15 mg kg^{-1} *i.v.*