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The 2014 guidelines for post-operative pain management

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ORGANISATION OF ACUTE PAIN MANAGEMENT SYSTEM

The success of a surgical procedure is conditioned by many factors, including appropriate pain control, early ambulation and rehabilitation after surgery, which directly translates into three relevant elements mentioned in numerous publications, i.e., hospitalisation length and costs as well as patient satisfaction. There are many mechanisms of post-operative pain; therefore, various approaches to post-operative analgesia should be used to improve pain relief and reduce the number of complications.

Although the mechanisms of pain are increasingly well understood and novel, safe analgesics and techniques of anaesthesia are introduced, the level of post-operative pain relief in the developed countries is still unsatisfactory. Inadequate (ineffective) post-operative pain control can lead to adverse consequences for patients, i.e., the development of chronic pain, immunosuppression, poorer healing of surgical wounds, and adrenergic activation and its consequences in the form of coronary incidents or gastrointestinal obstruction; moreover, lack of mobility can result in thrombosis and embolism. These complications affect hospital functioning, which leads to decreased patient satisfaction, a worse reputation for the hospital, prolonged hospitalisations, higher incidence of re-surgeries and re-admissions, and higher costs for care and treatment, as well as higher numbers of claims and compensations [1, 2].

A questionnaire study carried out in Danish hospitals revealed that patients were not informed about the available methods of post-operative analgesia. Moreover, the intensity of pain was not evaluated according to any scale in 55% of patients on post-operative day 1, in 71% on post-operative day 2 and in 84% on post-operative day 3. In the majority of patients (75%), pain was relieved using opioids. Non-opioid drugs were not used in appropriate doses, and multimodal therapy was applied in a low percentage of patients, which resulted in the development of nausea and vomiting in 20% of respondents. Although the guidelines regarding acute pain management are available in Denmark, only 14% of patients were treated in accordance with their principles [3].

These guidelines (recommendations) have been prepared to increase and update knowledge levels and are the source of the information that should be used while implementing the principles of proper pain control in hospitals. The guidelines suggest that pain therapy in hospitals should be organised. The optimal solution is acute pain service (APS), i.e., an interdisciplinary organisational structure of various competences and responsibilities. The major functions of

APS are to inform patients about possible analgesic therapy after surgery, to continuously train medical personnel, to use the rules of analgesia in accordance with the newest guidelines, to monitor the intensity of pain multiple times per day, and to evaluate the incidence of complications. The above principles are in fact the guidelines required in order to receive the "Hospital without pain" certificate. In order to ensure that good practices are continued, the certificate is granted for 3 years. After that period, a given hospital has to be re-certified, which motivates the personnel to maintain suitable levels of pain management in the hospital. In Great Britain, audit studies were conducted in two stages. The second audit demonstrated reduced percentages of patients with severe pain, lower incidences of severe complications (e.g., opioid-induced respiratory depression) and an increase in the employment of nurses who specialised in pain [4].

THE MULTIMODAL CONCEPT OF ACUTE PAIN RELIEF

The development of post-operative pain is an extremely complex process. During surgery, the mediators of inflammation are released, which include histamine, leukotrienes, prostaglandins, cytokines, bradykinin and others. The above mediators intensify hyperalgesia at the place of injury and in the surrounding tissues.

The afferent neurons release stimulating amino acids (glutamates, aspartates) or peptide neurotransmitters (substance P, neurokinin, calcitonin, cholecystokinin and somatostatin), which affect the conversion and modulation of pain. The nociceptive activity of the spinal cord is transmitted to the higher centres in the brain where pain is modulated mediated by endogenous opioids, noradrenaline, and 5-hydroxytryptamine (serotonin, 5-HT). The above-mentioned substances are capable of enhancing or inhibiting pain. In accordance with its assumptions, multimodal analgesia should be administered at various levels where the pain stimulus is formed and processed (peripheral, spinal cord, medullary centres) and thus is more effective than are methods that address only one of the levels mentioned.

The multimodal form of pain management also involves acting on each of its components. Non-steroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors affect the transduction of pain, regional nerves block pain transmission, and opioids, clonidine, ketamine, and gabapentin reduce its perception, whereas antidepressants impact the CNS reaction. The combination of drugs from these groups is particularly recommended in cases of extensive surgical procedures with a high risk of chronic pain.

PERSISTENT POST-OPERATIVE PAIN

Severe persistent post-operative pain is one of the major reasons for prolonged hospitalisations or readmissions. Persistent post-operative pain is defined as a pain that persists for longer than 3 months after surgery (trauma) and most commonly occurs after inguinal hernia repairs (30%) and thoracic surgeries (50%). The occurrence of pain before surgery in places not connected with the procedure or pain that persists for over 7 days after surgery are the factors that predispose patients to developing chronic pain. From the clinical point of view, predisposing factors also include preoperative physical disability or obesity. The other factors that predispose to the development of chronic pain are: prolonged duration of surgery, the surgical technique used (e.g., laparoscopy vs. laparotomy), and the surgical methods or types of implants applied, all of which are directly associated with the extent of surgical trauma and the development of inflammation. Moreover, regional, preventive and pre-emptive anaesthesia are important for preventing chronic pain [5].

ANALGESIC ADMINISTRATION ROUTES

In the immediate post-operative period, it is strongly that no drugs be administered intramuscularly or subcutaneously in cases of hypothermia and hypovolaemia because this practice can lead to uncontrolled (changeable) absorption of drugs and poor analgesic efficacy. After surgeries associated with a high intensity of post-operative pain, during the initial post-operative period, it is recommended to use analgesic therapy based on intravenous infusions of non-opioids and/or opioids; the agents should be well titrated prior to administration to ensure the minimum effective analgesic concentration (MEAC) and its maintenance throughout the period of analgesic therapy.

PRE-EMPTIVE ANALGESIA

Because of the findings of many studies on pain and those from the field of neurophysiology, a strategy for preventing the development of perioperative hypersensitivity has been elaborated. It aims at minimising or eliminating the increased afferent nociceptive stimulation of the central nervous system that can develop during surgery, which limits the development of peripheral and central sensitisation. This type of management is known as pre-emptive analgesia. To induce the effect of pre-emptive analgesia, it is recommended to use various groups of drugs and various methods, e.g., block anaesthesia, gabapentinoids (gabapentin, pregabalin), opioids, non-steroidal anti-inflammatory drugs, paracetamol, metamizole, NMDA receptor antagonists (ketamine, dexmedetomidine), alpha-2 receptor agonists (clonidine, dexmedetomidine), tricyclic antidepressants (e.g., doxepin) or cytokine activation modulators (e.g., i.v. lidocaine).

NON-OPIOID ANALGESICS

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

This group of drugs includes COX-1 and COX-2 inhibitors. The efficacy of these two types of COX inhibitors after surgeries accompanied by mild and moderate pain is comparable. Neither is preferable, and thus, the choice is determined by adverse side effects, contraindications and the forms available. In cases of classic NSAIDs used in patients at risk of gastrointestinal side effects, it is important to add a proton pump inhibitor. The analgesic effect of specific COX-2 inhibitors is similar to that of traditional NSAIDs; however, COX-2 inhibitors cause fewer adverse effects and less strongly affect blood clotting. Celecoxib, parecoxib and etoricoxib can be used in patients who are at increased risk of gastrointestinal side effects after surgical procedures accompanied by increased blood loss or in patients with aspirin-induced asthma.

METAMIZOLE

The current guidelines devote more attention to this drug because of the variety of contradictory and controversial reports that resulted in limitations on its use and even its abandonment in some regions of the world. However, this opinion has recently been verified, which is evidenced in the guidelines for pain management in some Scandinavian countries. The current literature demonstrates its efficacy in acute pain therapy and its favourable profile regarding adverse side effects, particularly compared with NSAIDs [6].

Metamizole has been available worldwide since 1922. It belongs to the most commonly prescribed analgesics (in 2009, over 110 million daily doses were prescribed in Germany) [7]. It is an analgesic, antipyretic therapeutic agent from the group of pyrazoline derivatives. The agent is administered as a "prodrug" orally, rectally, intramuscularly or intravenously. The absorption after oral administration is quick and nearly complete, with 85% bioavailability and time till maximum plasma concentration (Tmax) of 1.2–2.0 h. Its analgesic effect begins within 30 min after intravenous administration and last for approximately 4 h. In the body, metamizole is hydrolysed to active metabolites: 4-methyl-amino-antipyrine (4-MAA) and aminoantipyrine (AA). The above metabolites are mainly excreted via the kidneys, and their half-life is 2.5–3.5 h. In cases of severe toxicity/overdose, metamizole can be removed from the blood using haemodialysis. The exact mechanism of its action is unknown. The findings from animal studies reveal that metamizole inhibits cyclooxygenase (COX) in peripheral tissues as well as the central nervous system. COX is involved in converting arachidonic acid into prostaglandins and thromboxane (COX-i) or into prostaglandins and prostacyclin (COX-2). Specific prostaglandins, particularly prostaglandin E2, play an important role in the development of pain and fever. It is known that in the case of classic NSAIDs, COX activity is blocked by competing with arachidonic acid for the COX-binding site. In contrast, metamizole does not attach to this binding site but rather, inhibits the release from other binding places of free radicals, which are necessary to initiate COX-mediated arachidonic acid metabolism. In particular, metamizole appears to inhibit COX-2. Its anti-inflammatory effects are less potent than those of typical NSAIDs. Strictly speaking, metamizole cannot be considered an NSAID; its profile of adverse side effects does not allow it to be included in this group of drugs. Moreover, the spasmolytic properties of metamizole distinguish it from NSAIDs and opioids; these properties most likely induce direct dilating effects on smooth muscles [8]. A recently published meta-analysis has revealed that metamizole is an effective agent for alleviating post-operative pain [9]. In placebo-controlled studies, metamizole reduced pain intensity by 50% in over 70% of patients. Additionally, the requirement for another "rescue analgesic drug" was reduced from 34 to 7%. Studies that compared metamizole with tramadol demonstrated a similar or even more potent analgesic effect of metamizole after extensive abdominal and urological surgeries. These studies' findings showed that metamizole caused fewer gastrointestinal side effects and contributed to higher patient satisfaction. Indirect comparative studies disclosed that 500 mg of metamizole was as effective as 400 mg of ibuprofen and more effective than 1000 mg of paracetamol. Owing to its spasmolytic properties, metamizole is extremely effective in relieving renal colic pain and post-operative pain after abdominal, gynaecological and urological surgical procedures [10].

The mechanism underlying idiosyncratic, drug-induced agranulocytosis has not been fully elucidated, yet the condition is likely to be caused by drug-dependent autoantibodies acting against circulating neutrophils or their precursors in the bone marrow. It is characteristic that the reaction occurs within a number of or weeks after the initiation of metamizole use [11]. The relationship between the use of pyrazoline derivatives and agranulocytosis was first described in the British Medical Journal in 1952. According to the paper published there, the risk of agranulocytosis with amidopyrine was 0.86%. Later studies reported much lower incidences of metamizole-induced agranulocytosis. Their findings are summarised in Table 1. The high variability of agranulocytosis incidence is worth noting. This variability can be partly explained by difficulties in collecting reliable data for calculating the incidence of metamizole-induced agranulocytosis as well as the data regarding the total amount of metamizole used. Incidences lower than those given in the table are highly vulnerable to accidental changes [12]. According to the WHO data, the global incidence rate is approximately 1 per 110 million weekly doses.

Table 1. Studies on metamizole-induced agranulocytosis

Reference	Estimated incidence	Country	Study description
Basak GW, 2010	0.08/million daily doses	Poland	Prospective observational study in haematological centres; 3 patients with agranulocytosis or aplastic anaemia with a total number of 12 579 196 daily doses of metamizole
Ibanez L, 2005	0.56/million daily doses	Spain	Prospective controlled study in 17 haematological centres; incidence calculated for the total population
Maj S, 2004	0/19 million daily doses	Poland	Prospective observational study in haematological centres; no patients with agranulocytosis with a total number of 18 716 682 daily doses of metamizole
Maj S, 2002	0.2/million daily doses	Poland	Prospective observational study in haematological centres; 6 patients with metamizole-associated agranulocytosis out of a total number of 23 656 862 daily doses of metamizole
Hedenmalm K, 2002	1/1439 patients	Sweden	Estimated incidence based on the number of adverse effects reported to the appropriate board and total consumption of metamizole based on pharmacy data
Backström M, 2002	1/31 000 hospitalised patients	Sweden	Estimated incidence based on the number of adverse effects reported to the appropriate board and the total consumption of metamizole based on data from pharmacies and hospitals
Andrade SE, 1998	6/100 million weekly doses	international	Meta-analysis of excess mortality (and its causes) attributable to the use of analgesics; the total number of excess deaths attributable to metamizole was 25 per 100 million weekly doses
IAAAS study group, 1986	1.1/million weekly doses	international	Controlled study demonstrating different relative risks in different countries, ranging from 0.8 in Israel and Hungary to 23.7 in Germany and Spain
Varonos DD, 1979	1/133 000 466 000 applications	Greece	Retrospective study that identified 24 individuals with agranulocytosis; for 15 of them, there was a possible connection with the treatment administered. Incidence rates were calculated based on the total amount of metamizole sold on the assumption that all 15 cases of agranulocytosis were caused by metamizole

Contrary to NSAIDs, metamizole is associated with a low risk of gastrointestinal complications. According to a meta-analysis of epidemiological studies concerning severe adverse side effects after aspirin, diclofenac, paracetamol and metamizole in the years 1975–1995, the excess mortality attributable to agranulocytosis, aplastic anaemia, anaphylaxis and severe gastrointestinal complications was 185 per 100 million weekly applications of aspirin, 592 per 100 million weekly applications of diclofenac, 20 per 100 million weekly applications of paracetamol and 25 per 100 million weekly applications of metamizole [13]. Moreover, the meta-analysis clearly showed that the mortality rate attributable to bone marrow aplasia did not differ from that caused by metamizole administration. Despite the above findings, diclofenac is recommended for acute and chronic pain management worldwide [13].

Although metamizole dilates the vascular smooth muscle, it can reduce arterial pressure, especially when its intravenous administration is rapid. No adverse effects of metamizole on the cardiovascular system or kidneys were observed; furthermore, it did not significantly affect platelet aggregation. The contraindications for the use of metamizole include: allergies to metamizole and/or NSAIDs, severe arterial hypotension, reduced volume of circulating blood (hypovolaemia) or shock, acute intermittent porphyria, glucose-6-phosphate dehydrogenase deficiency, age < 3 months to treat fever and < 15 years to relieve pain, and pregnancy and breast feeding. In cases of renal and liver failure, the dose of metamizole should be halved because of the decreased metabolism and elimination.

Notably, today's approach to combining metamizole with other analgesics has changed. Metamizole is found to act synergistically with opioid analgesics; moreover, it can be combined with NSAIDs and paracetamol. This changed attitude towards the combinations of metamizole with NSAIDs and paracetamol was connected with the identification in 2012 of new active metamizole metabolites that exert inhibitory effects on COX-1 and COX-2. Additionally, they show affinity to cannabinoid receptors (CB 1 and CB 2), induce analgesia at the spinal cord and brain levels and increase the activity of the descending antinociceptive system [14].

PARACETAMOL (ACETAMINOPHEN)

Paracetamol is the most popular and most commonly used antipyretic and analgesic worldwide, mainly because of its low risk of adverse reactions and proven analgesic efficacy. There are a number of hypotheses regarding the cen-

tral effects of paracetamol that could explain its analgesic efficacy. According to one of them, paracetamol inhibits the central activity of COX-2; its possible effects on the next isoform of cyclooxygenase, COX-3, are being disputed. Warner and colleagues (10) described two COX isoenzymes — partial COX-1 (pCOX-1) and COX 3 — as occurring predominantly within the human cerebral cortex and heart. Unlike pCOX-1, COX-3 shows cyclooxygenase activity to be inhibited by paracetamol. It is believed that COX-3 is likely to be encoded by the same gene that encodes COX-2 but differs in its molecular characteristics. COX-3 would then be a variant of COX-2 that is highly susceptible to paracetamol-induced inhibition. Moreover, paracetamol was suggested to affect the antinociceptive serotonergic system, stimulating the activity of the descending serotonergic pathways (5-HT). The above hypothesis was recently supported by the findings of a clinical trial that demonstrated that the combined use of paracetamol and one of two antiemetic drugs — the 5-HT_3 antagonists granisetron and tropisetron — inhibited analgesic action of paracetamol. The other hypotheses suggest antagonistic effects on the N-methyl-D-aspartate (NMDA) receptor or on the mechanism of action connected with nitrous oxide. Generally, the preparation of paracetamol for parenteral administration markedly increased its use as a perioperative analgesic that can be administered to patients who cannot take oral medications. Because the cost of parenteral administration is much higher than that of oral preparations, it is recommended to change the administration route to oral as quickly as possible. Paracetamol taken in the therapeutic dose is well tolerated and causes slight side effects. There were no statistically significant differences found in the incidence of adverse side effects between paracetamol (975/1000 mg) and a placebo. Organ toxicity results mainly from overdose or chronic use, which is not the case in the post-operative period. Paracetamol is metabolised predominantly in the liver, and therefore caution should be exercised in patients with active liver disease, long-term alcohol abusers and those with limited glutathione stores. In these cases, as with overdose, hepatotoxicity is caused by oxidised N-acetyl-p-benzoquinone imine (NAPQI) metabolite, which constitutes only 5% of paracetamol metabolites and is usually bound by glutathione. If the glutathione stores were depleted after overdose or were deficient from the very beginning, NAPQI binds liver proteins, causing necrosis of the central part of the hepatic lobules, which develops over a period of 4 to 14 days. It is generally believed that the causes of depleted glutathione levels include starvation, malnutrition, HIV infection and regular alcohol consumption; however, the importance of these factors is increasingly being questioned. Apparently, neither alcohol abuse nor malnutrition increases the risk of hepatotoxicity provided that the paracetamol is administered in therapeutic doses. In overdose cases, the affected patients are at risk of more severe intoxication than are those who are unexposed to the risk factors. Paracetamol can very occasionally lead to haemolysis in homozygotes with G6PD deficiency. Moreover, its unexpected, dose-dependent effect on platelet aggregation has been demonstrated and is most likely connected with a poor COX-1 inhibiting effect. Toxic effects on other organs are slight, although such cases have been reported. Nephrotoxicity has been extremely rare since the prodrug phenacetin was withdrawn. In patients undergoing cardiac surgeries, the cardiac index has been found to be decreased by 10%. Regarding its efficacy, scientific evidence for paracetamol as a post-operative analgesic is favourable; Barden and co-workers [15] noted that single doses of paracetamol were more effective for the treatment of post-operative pain compared with a placebo. Furthermore, paracetamol is a useful component of multimodal analgesia, which was demonstrated in combinations with various opioids including codeine, tramadol and morphine. The results obtained from volunteers suggest that the above is partly connected with the fact that paracetamol decreases central sensitisation [15–19].

OPIOID ANALGESICS

Three types of opioid receptors are distinguished: MOR (formerly mi — μ), DOR (delta — δ) and KOR (kappa — κ). Based on their methods of stimulation, opioids can be divided into: full agonists, characterised by relative selectivity for μ receptors, which reflects their similarity to morphine, partial agonists, which show partial agonism mainly for μ receptors, and opioids of mixed agonistic-antagonistic properties, which interact with more than one class of receptors and can therefore act as agonists for one receptor and as antagonists for the other. The most important opioids used in acute pain management include morphine, oxycodone, fentanyl, nalbuphine, buprenorphine and tramadol.

Opioids belong to the constant repertoire of options for pharmacological relief of moderate-to-severe post-operative pain. Their doses should be tailored individually in consideration of pain evaluation scores and possible adverse side effects. Post-operative pain therapy with opioids should be organised pursuant to the choice of opioid, the time of administration, the intervals between doses and the route of administration.

PATIENT-CONTROLLED ANALGESIA (PCA)

Post-operative pain relief using PCA should be initiated with a saturating dose of opioid in order to provide the maximum analgesic efficacy. It is recommended to administer the saturating dose (titration) while the patient is still in the post-operative surveillance room until the level of pain intensity ≤ 4 (according to the 10-degree scale) has been

achieved, simultaneously considering the respiratory rate, which should not be lower than 12 min^{-1}. After titration, the PCA system is initiated. It is not recommended to use a basic infusion because of the risk of respiratory depression, the incidence of which is estimated at 0.09–0.5%, particularly in elderly patients, those with sleep apnoea or COPD and newborns. It should be remembered that opioid receptor antagonists, such as naloxone or naltrexone, are the treatment of choice for respiratory depression after opioids. However, their time of action is shorter than of opioids and the risk of "re-narcotisation" is very real [20].

Morphine is an opioid used to treat severe pain and a standard to determine the action of other opioids administered orally or by injection. Morphine should be applied with caution in individuals with advanced kidney failure because of the possible accumulation of its active metabolite (morphine-6-glucuronide), which can cause respiratory failure.

Oxycodone, in its various forms, has wide possibilities for adjusting the required efficacious therapy to suit its therapeutic possibilities. The drug is available in intravenous, oral and other forms. The combination of this drug in its intravenous controlled-release form, which acts immediately, is increasingly common, as is the so-called "step down", i.e., the withdrawal of epidural or intravenous analgesia after 1–2 days of use. The controlled-release form of oxycodone can be used to treat chronic pain similar to extended-release morphine. The advantage of morphine is that equilibrium in the plasma is quickly obtained owing to oxycodone's two-phase absorption model, which means that the initial rapid absorption — the first phase of action — occurs after approximately 40 min and is followed by slow drug release over 12 hours at the constant serum concentration of the analgesic that is being maintained. Because of this action, oxycodone can be included in the group of potent drugs used for post-operative pain relief [21].

In comparing morphine and oxycodone, it should be remembered that both drugs have no upper limit dose. In oral therapy, both controlled-release morphine and oxycodone must be administered at 12-hour intervals. Titration of the oral dose and calculations of the rescue dose are identical to those of extended-release and parenteral morphine. The bioavailability of oral oxycodone is much higher than that of morphine, i.e., 60–80%, which results from the reduced effect of the first pass through the liver compared with morphine. Oxycodone administered orally is roughly twice as strong as oral morphine. The intravenous route of opioid administration (morphine, oxycodone, fentanyl) selected during the first post-operative phase, with the possibility of changing to oral administration, is ideal for severe post-operative pain therapy, inter alia, for eliminating the subcutaneous and intramuscular routes.

The skilful use of the intravenous route in the initial post-operative period followed by transferring to therapy with a controlled-release drug is solely analgesic management aimed at achieving the minimum effective analgesic concentration (MEAC) in blood serum and its maintenance throughout the pain therapy [22].

Oxycodone and other opioids of similar analgesic action are relatively commonly used for the therapy of moderate-to-severe pain when there is fear of complications associated with the supply of NSAIDs. The adverse side effects of opioids, such as drowsiness, nausea, constipation, impaired or delayed miction, or pruritus, can be eliminated or substantially alleviated by using multimodal therapy. Some side effects (nausea, vomiting, pruritus or excessive sedation) are less common during oxycodone therapy compared with morphine (most likely owing to the stimulation of KOR). The change from intravenous to oral opioid administration enables effective and safe pain therapy and hence, earlier rehabilitation and reduced hospitalisation length. The additional asset of controlled-release oxycodone, stressed in many publications, is its high analgesic efficacy combined with its convenience for the patient and personnel (1 tablet administered every 12 hours). The patient's satisfaction is additionally affected by the fact that pain does not disturb nocturnal sleep and rest. However, it should be remembered that none of the controlled-release preparations can be used "on demand", mainly because the time needed to achieve the peak analgesic action is 4 hours [23–28].

The efficacy and usefulness of oral opioid therapy were demonstrated by American authors in a group of patients after cardiac surgeries; the study compared oral therapy based on the combined use of oxycodone with naloxone at 20 mg every 12 hours with morphine PCA (the basic infusion 0.3 mg h^{-1}, bolus dose 1 mg, lockout 5 min). The authors concluded that oral opioid therapy was easier to use and cheaper although the analgesic efficacy of both methods was comparable [29].

Fentanyl is a synthetic opioid whose action is 50–80 times stronger than that of morphine. The onset of action is quick (10 sec. after i.v. administration). The time of action after the administration of 0.1 mg is 1–1.5 h. Fentanyl is recommended when rapid, efficacious analgesia is required; however, owing to its short action, it should be used in continuous infusions or using PCA. Fentanyl can be used in patients with impaired renal functions because it is metabolised into inactive metabolites in the liver [30].

Tramadol, one of the weak agonist opioid receptors, is a synthetic analogue of codeine that acts centrally. It can be successfully used intravenously and parenterally for moderate and severe pain. The analgesic potency of tramadol compared with other opioids is as follows:tramadol:nalbuphine 5:1; tramadol:fentanyl 979:1; tramadol:oxycodone 8:1, tramadol:morphine 10:1.

The increased analgesic action results from the inhibition of noradrenaline reuptake in neurons and an increase in serotonin release. In individuals treated with tramadol in recommended doses, there have been cases of seizures. This risk can increase if the recommended daily dose (400 mg) is exceeded and in patients with a history of seizures or those who are simultaneously taking serotonin and noradrenaline reuptake inhibitors, tricyclic antidepressants, anti-psychotic drugs or other agents that reduce the seizure threshold. Tramadol administered with other drugs that increase serotonin concentrations can induce serotonin syndrome. Tramadol's capacity to induce respiratory depression is minimal, and therefore, it can be recommended for labour analgesia, pain relief in children, short-term and day case surgeries and after trauma. Tramadol is extremely efficacious combined with metamizole for pain management in renal or biliary colic. The recommended dosage of tramadol in PCA is as follows: bolus dose — 30 mg, lockout — 5 min, infusion — 0.35 mg kg^{-1} h^{-1} [31].

Although tramadol has a low capacity to induce addiction, its long-term use may result in tolerance as well as psychological and physical dependence. Tramadol is a component of preparations combined with non-opioids, e.g., paracetamol [32].

Codeine is a natural opioid and one of the major opium alkaloids. It shows low affinity to opioid receptors; its analgesic action is provided by its active metabolite, morphine, to which form approximately 10% of the codeine dose administered is converted. The conversion of codeine to morphine is mediated by the isoenzyme CYP2D6. Approximately 10% of Caucasians slowly metabolise CYP2D6 substrates; therefore, codeine can be ineffective in this population. The doses for relieving pain are 30–60 mg administered every 4 h until the maximum daily dose of 240 mg is achieved. Similar doses are used in combinations with paracetamol, yet owing to the additive action, the analgesic potency is higher. In Poland, there are no single-component preparations available. Examples of the available combined drugs are Dafalgan and Efferalgan. A half-synthetic derivative of codeine of similar pharmacological properties is **dihydrocodeine**. Its bioavailability after oral administration is approximately 20%; it is metabolised in the liver by the cytochrome CYP2D6 into dihydromorphine and others. The analgesic action after oral administration of its unmodified-release form is comparable with that of morphine. Extended-release dihydrocodeine (e.g., DHC Continus) administered twice a day every 12 h is used to treat severe chronic pain, including cancer pain. The unmodified-release forms unavailable in Poland are often used in the EU countries combined with paracetamol. Dihydrocodeine, similarly to codeine, shows the upper limit effect, which means that increasing its dose does not intensify the analgesic action but only enhances side effects [33].

Buprenorphine is a partial agonist and is similar to opioids of mixed agonistic-antagonistic properties, such as nalbuphine or butorphanol. Ago-antagonists have limited use for chronic pain owing to their dose-dependent, psychosis-mimetic action; moreover, their use in patients who are addicted to morphine or other full MOR agonists can cause withdrawal owing to their antagonistic effects on MOR. The drugs in question are characterised by reduced addictive potential compared with that of full agonists. In Poland, only parenteral forms of buprenorphine are currently available (sublingual tablets and patches). The parenteral form of buprenorphine, unavailable in our country, is recommended worldwide. In a dose of 5–15 μg kg^{-1}, parenteral buprenorphine provides analgesia comparable with that of i.v. morphine for up to 13 hours.

Sublingual buprenorphine is recommended for maintaining post-operative analgesia in select clinical situations. It is an extremely useful post-operative analgesic in patients who once abused opioids. Furthermore, buprenorphine is efficacious as a monoanalgesic in 80% of patients after cholecystectomy.

Transdermal buprenorphine is effective owing to its high solubility in fat. It is mostly recommended for chronic pain, but according to numerous reports from various European countries, this form is also useful for acute pain. Transdermal buprenorphine is available in the doses of 35, 52.5 and 70 μg h^{-1} and lasts for 3 days. The onset of action is after 12–24 hours. The drug is useful and recommended in patients with kidney failure. Because of its long action, it can be used in the elderly. Buprenorphine prevents hyperalgesia and hence can be used in patients with chronic pain who must undergo surgeries (or after trauma). Experimental studies have demonstrated that its prevention of hyperalgesia was stronger than the analgesic effect induced by any direct effects on MORs. Thus, buprenorphine can be of significant importance in preventing or reducing central sensitisation as well as preventing chronic post-operative pain.

When using buprenorphine, attention should be paid to other drugs taken by the patient. Drugs such as opioids, sedatives, hypnotics, antidepressants and others can induce or inhibit the isoenzyme of cytochrome P450, which can increase the central effects of buprenorphine. Great caution should be exercised when benzodiazepines are simultaneously used because this combination can lead to intensified sedation, respiratory depression or even death [34].

Nalbuphine is a KOR agonist and MOR antagonist. As an MOR antagonist, it prevents typical side effects associated with MOR stimulation (respiratory depression, addiction, euphoria, bradycardia, pruritus, immunosuppression, nausea and vomiting, impaired peristalsis, weakened muscular tone of the urinary bladder). The drug is thus

a compromise between adequate analgesia and safety of use. It is recommended for weak to moderately severe pain. Nalbuphine is not recommended for patients who addicted to opioids and being treated chronically with opioids/MOR agonists (withdrawal symptoms, including strong pain, can be substantially exacerbated); moreover, the combination of nalbuphine with other opioids/MOR agonists is not advocated.

Because nalbuphine is metabolised in the liver and excreted through the kidneys, great caution should be taken when using the drug in patients with failure of these organs. Although a dose of 10 mg of nalbuphine can cause respiratory depression, similar to 10 mg of morphine, unlike with morphine, nalbuphine shows the upper limit effect. The upper limit of respiratory depression occurs at a dose of approximately 30 mg, and the upper limit analgesic effect is observed at 50 mg; therefore, other opioids that do not show the analgesic upper limit are recommended in individuals with severe pain. Nalbuphine is an acceptable alternative for labour pain relief, provided that the foetal heart rate can be monitored. PCA is the method of choice for labour analgesia. In adults, i.v. doses of 0.1–0.3 mg kg^{-1} are used, without exceeding 20 mg. The maximum action is observed 2–3 minutes after intravenous administration. The dose can be repeated after 3–6 hours. In PCA, the following doses are recommended: bolus, 1–3 mg and lockout, 6–10 minutes. When continuous infusions are required, the doses are 0.04–0.32 mg kg^{-1} h^{-1} [35].

Until recently, the combination of potent opioids was not recommended; however, considering the findings of recent experimental and clinical studies, it is difficult not to agree with opposite opinions. In select clinical situations, some opioids can be combined to achieve a synergistic analgesic effect. The synergism of analgesic action results from the effects on various types of opioid receptors (MOR, KOR, DOR) and differences in opioid pharmacokinetics. In piano therapy, the synergism of analgesic action is observed in the case of combining morphine with oxycodone as well as fentanyl. When these opioids are combined, various types of opioid receptors are used as well as different pharmacokinetic parameters, particularly differences in blood-brain barrier penetration. Morphine is and MOR agonist whereas oxycodone affects MORs and acts agonistically on KORs, which widens the spectrum of analgesic action, especially in visceral pain. It is notable that oxycodone can exert analgesic effects by antagonising nociceptive activity, which additionally widens the spectrum of this combination. The pharmacokinetic differences in the opioids used in combination are also important. Fentanyl and oxycodone pass through the blood-brain barrier significantly more rapidly than does morphine; therefore, the central effect of their action is observed more quickly. As mentioned earlier, in clinical practice, the synergism of this action is achieved by combining potent opioids, except for fentanyl with methadone and nalbuphine with MOR agonists. Fentanyl and methadone are metabolised by CYP 3A4; they show competing interests, which increases the risk of prolonging methadone half-life and of heart rhythm ventricular disorders. Nalbuphine, in contrast, is a KOR agonist and MOR antagonist, which evidently results in the inefficacy of combining it with MOR receptors [36, 37]. The idea of combining opioids dates back to the 1990s, when researchers suggested that combining two opioids could result in a synergistic analgesic effect while at the same time reducing the side effects that could develop from the separate use of each. Researchers recommend the combination of morphine and oxycodone. The efficacy of dual-opioid therapy is determined by the affinity of both opioids to various receptors. In the case of the above combination, Bruce and colleagues [36] demonstrated reduced percentages of the following side effects: nausea by 46%, vomiting by 17%, dizziness by 45%, sedation by 75% and disorders of peristalsis by 60%. This last complication is particularly important because the average total cost of care of patients with post-operative paralytic obstruction is estimated at $4,880-36,152 per patient. By providing good clinical effects, dual-opioid therapy (morphine with oxycodone) reduces side effects and thus contributes to lowering care-related costs [36].

In practice, buprenorphine (a partial MOR agonist) administered in its transdermal therapeutic system (TTS) form at 140 μg h^{-1} can be combined with MOR agonists. Combining weak opioids (codeine, dihydrocodeine, tramadol) with potent ones is, however, not recommended because the former are characterised by the upper limit effect, which can reduce the efficacy of the latter. Admittedly, there are animal studies that reveal the synergism of action between tramadol and potent opioids; however, this effect was not confirmed in humans. Advocates of combining strong opioids with tramadol emphasise higher analgesic efficacy, which can, however, result from the fact that tramadol, which affects opioid receptors, inhibits serotonin reuptake in the descending pain control pathways [38, 39].

USE OF OPIOIDS FOR CENTRAL BLOCKS

Opioids can be used with good analgesic effects as adjuvants in central blocks. The recently recommended and increasingly used continuous subarachnoid anaesthesia, continued in the post-operative period, enables very good pain control and active rehabilitation after orthopaedic and abdominal surgeries using small concentrations of local anaesthetics and opioids. The recommended dose of morphine for subarachnoid analgesia should be 50–100 μg and does not exceed 300 μg. Lipophilic opioids, such as fentanyl or sufentanil, are recommended for labour analgesia, Caesarean section anaesthesia and ambulatory surgical

procedures. The dose of morphine for epidural analgesia should be 2.5-3.5 mg during the first 24 hours after surgery. When opioids are used in central blocks, patients should be suitably supervised; ventilation (respiratory rate and depth), blood oxygenation (pulse oximetry) and the degree of sedation should be assessed [40].

OPIOID-ASSOCIATED COMPLICATIONS

Although the efficacy of opioids for post-operative pain therapy is undisputable, side effects and possible complications associated with their use should be considered. A large study demonstrated that in 12% of patients who received post-operative opioids developed side effects that were strictly connected with their use and that directly prolonged their hospitalisations and increased their costs. The higher the doses of opioids, the higher the risk of complications. The complications were more common in certain groups of patients (the elderly, patients with COPD, sleep apnoea, and asthma and obese patients). The only correct strategy to eliminate complications is multimodal preventive analgesia to achieve the effect of reducing the opioid doses [1].

EPIDURAL ANALGESIA FOR POST-OPERATIVE PAIN MANAGEMENT

Recent data indicate that the benefits of epidural anaesthesia are not as significant as was earlier believed. Although the efficacy of pain alleviation using this method is excellent and the cardiovascular benefits and reduced incidences of pulmonary complications in high-risk patients undergoing extensive vascular, thoracic and cardiac surgical procedures are significant, the techniques of epidural anaesthesia are less commonly used. There are a number of reasons that this invasive, expensive and laborious technique has decreased in popularity:

- few data demonstrate reduced perioperative mortality,
- there is unconvincing evidence for reduced mortality in low- and medium-risk patients,
- there have been advances in the surgical techniques used for short-term procedures,
- the necessary rapid ambulation of patients after surgery and the institution of early rehabilitation,
- the widespread use of antithrombotic prophylaxis,
- accumulating evidence for the efficiency of less invasive methods of regional analgesia even for extensive procedures,
- the lack of convincing evidence for its cost-effectiveness, even though the method has been used for decades,
- the increasing number of compensation claims associated with severe neurological complications.

Epidural anaesthesia is still the gold standard for labour pain relief. The views on its use in orthopaedics and thoracic surgery are divided because the use of alternative methods, such as continuous peripheral nerve blocks or infiltration anaesthesia, in these fields is markedly increasing [41].

PERIPHERAL NERVE BLOCKS

The guidelines for post-operative pain management clearly emphasise the importance of multimodal analgesia, the essential element of which should be local anaesthesia (peripheral nerve blocks) whenever possible. The indications for continuous peripheral nerve blocks for relieving perioperative pain in hospitalised patients and those undergoing ambulatory anaesthesia have expanded greatly. The techniques in question are used not only in patients undergoing upper and lower limb surgeries but also to provide perioperative analgesia in individuals undergoing abdominal plastic, thoracic, urological, gynaecological and trauma surgical procedures.

The protocols regarding local anaesthetics and their adjuvants should take into consideration the patient's condition before and after surgery, the nature and severity of surgery-related stress and the chances for quick recovery. The use of continuous peripheral nerve blocks allows for decreasing opioid consumption and reducing their adverse side effects, accelerating recovery and in many cases, decreasing the length of hospitalisation. Continuous peripheral nerve blocks were found to be a safer alternative to epidural anaesthesia in patients who were administered antithrombotic prophylaxis.

The indications for continuous peripheral nerve blocks include the relief of perioperative, trauma-induced, and chronic pain. Over a period of 12 years, the use of peripheral nerve blocks gained popularity for relieving acute post-operative pain after extensive orthopaedic and thoracic surgeries in adults and children, particularly in the context of the multimodal approach to post-operative pain management. Moreover, an interest in peripheral nerve blocks is growing owing to their potential anti-inflammatory effects and out of fear of severe complications from using central blocks in patients who are receiving anticoagulants.

In addition to the humanitarian and economic aspects of effective pain treatment, the use of continuous peripheral nerve blocks ensures better control of post-operative pain than does PCA and reduces opioid requirements and incidences of opioid-associated complications, enabling earlier ambulation and rehabilitation, reducing hospitalisation lengths and decreasing total treatment costs [42]. The majority of researchers agree that the opioid consumption is reduced by 40–70% when continuous peripheral nerve blocks are ap-

plied compared with PCA alone. Another asset of continuous peripheral nerve blocks in patients undergoing ambulatory anaesthesia is the reduced incidence of unanticipated readmissions, which markedly reduces their associated costs [43].

The "blind" placement of perinervous catheters (in the brachial plexus or paravertebral space) and other techniques associated with inducing paraesthesia that were used until recently have been replaced with stimulation techniques, or US (sometimes together with stimulation) to increase the efficacy of blocks [44]. The comparison of these techniques confirms that the use of US shortens the time needed to place the perinervous catheter, decreases the risk of vessel puncture, and reduces opioid requirements and the required volumes of local anaesthetics. The application of the new-generation LAs, e.g., ropivacaine, contributed to the reduction in toxic effects of these drugs. It is recommended to use various concentrations, infusion speeds and methods of administration for these drugs (continuous infusion, controlled by the patient, combination of both techniques, bolus) in order to determine the minimum analgesic dose and adjust it individually to given procedures [45].

It is difficult to establish one standard protocol for all patients that would consider the place of infusion, the pharmacokinetics of local anaesthetics, the procedure type, the need to use additional analgesics, the need for rapid recovery after orthopaedic surgeries and the expected length of hospitalisation. An example is ropivacaine, which is usually used in a concentration of 0.2%; in some cases, however, lower (0.1%) or higher (0.5%) doses are recommended.

The indications for continuous peripheral nerve blocks include extensive orthopaedic surgeries, extensive upper and lower limb traumas, re-implantation procedures within the upper and lower limbs, brachial, cubital, knee and ankle arthroplasty, and prolonged intensive rehabilitation of upper and lower limbs, as well as plastic, breast, thoracic, urological, abdominal and pelvic surgeries and multiple rib fractures (Table 2).

LOWER LIMB SURGERY

The indications for the continuous block of a given lower limb nerve depend on the procedure. In the majority of cases, it is sufficient to leave the catheter in the region of one nerve to control post-operative pain. After thigh or knee procedures, the catheter can be left in the region of the lumbar plexus and/or the femoral nerve. After foot or ankle surgeries, the catheter is left in the sciatic nerve in the popliteal region [20]. Studies have demonstrated the safety and effectiveness of continuous blocks of the lumbar plexus (from the posterior approach) in perioperative treatment after total hip arthroplasty [46]. The technique appeared to be more effective than continuous femoral blocks and intravenous PCA opioids [47]. Although continuous femoral blockade (block 3 in 1) is still recommended to relieve pain after total hip endoprosthesis, new findings demonstrate that lumbar plexus blocks are more beneficial [48].

TOTAL KNEE ARTHROPLASTY

To date, a number of continuous nerve block techniques have been suggested for perioperative pain relief after total knee arthroplasty, including continuous femoral and continuous lumbar plexus blocks [45]. Moreover, sciatic nerve blocks have been proposed. The combination of continuous femoral and sciatic nerve blocks is an alternative to epidural anaesthesia [49].

TALOCRURAL JOINT SURGERY

Continuous blocking of the sciatic nerve is recommended in such procedures for perioperative pain management. The lateral popliteal or posterior approach is advised.

UPPER LIMB SURGERY

For the majority of brachial surgeries, the interscalene approach is recommended [50, 51]. The continuous blockage (US is helpful in controlling the catheter location) provides more effective post-operative analgesia, reduces opioid requirements and improves the quality of sleep compared with single boluses [52]. For the majority of surgeries performed below the brachial joint, the supraclavicular, subclavicular and axillary approaches are equivalent alternatives (US provides the effectiveness of these methods). However, when the catheter must be maintained for a longer period after surgery, the subclavicular approach ensures better catheter stability and causes the patient less discomfort. Catheters placed from the supraclavicular and axillary approaches in order to provide prolonged post-operative analgesia should be tunnelled, which prevents their dislocation.

AMBULATORY SURGERY

In recent years, continuous blocks of select nerves in patients undergoing ambulatory surgeries are increasingly used worldwide. More and more thoracic, abdominal, pelvic and urological procedures will be carried out in the short-term system. According to experts, continuous paravertebral blocks provide good perioperative analgesia and cover the analgesic demands after thoracic (including breast), urological and abdominal surgeries [53].

THORACIC SURGERY

After thoracic surgeries, the paravertebral block (PVB) technique is recommended, which ensures pain control during coughing and at rest, lower opioid requirements, better ventilation, reduced post-operative nausea and vomiting and arterial pressure stability compared with epidural analgesia [54]. The use of antithrombotic drugs is a contraindica-

tion for epidural catheter placement, whereas their use does not exclude the possibility of using PVB. For thoracic procedures, the PVB catheter on one side of the thorax is placed at the T 4 level. The other indications for using a catheter for unilateral PVB include total or partial nephrectomy (T 8) or certain liver procedures (T 6). The bilateral placement of PVB catheters at the T 8–10 levels is recommended for analgesia after colon resections, abdominal liposuction, pancreas and liver resections, cystectomy and hysterectomy (including the removal of lymph nodes).

ANTICOAGULATION AND CONTINUOUS NERVE BLOCKS

There is much controversy regarding this issue. The newest guidelines of the American Society of Regional Anesthesia and Pain Medicine concerning regional anaesthesia in patients receiving anticoagulant and/or thrombolytic therapy recommend the use of the same guidelines for peripheral nerve blocks as for central blocks, but only in the case of the therapy combined with thrombolytic drugs [55].

In accordance with the trends observed in the worldwide guidelines, the anticoagulants used in prophylaxis should be distinguished from those recommended for treating the already existing risk of thrombosis and embolism. The reports of possible haemorrhagic complications following peripheral nerve blocks in patients administered venous thromboembolism (VTE) prophylaxis (there are few randomised and planned studies) do not report any severe haemorrhagic complications once the following rules are followed:

— blocks are performed 12 hours after the last dose of enoxaparin and 24 hours after the last dose of fondaparinux (when INR ≤ 2.0).
— VTE prophylaxis can be initiated after the block (unless complicated by blood vessel damage).
— the perirenal catheter can be removed, irrespective of the drug used for prophylaxis and its duration of action as well as the INR.
— the time the catheter is in place should be limited by the time necessary to control pain [56].

According to one of the recent reports, there were no haemorrhages in any of the 6935 patients who received both various peripheral nerve blocks and antithrombotic prophylaxis [57]. Similar data were reported in another study in which the use of continuous PVBs in patients who were receiving enoxaparin did not cause haemorrhagic complications [58].

ADJUVANTS IN MULTIMODAL THERAPY

The adjuvants in acute pain therapy are the drugs primarily used in monotherapy for other than acute pain indications but that have been demonstrated to be effective for acute pain relief. Their intravenous or enteral administration is recommended, combined with other analgesics, based on the concept of multimodal analgesia. This diverse group of adjuvants includes ketamine, clonidine, i.v. lidocaine and gabapentinoids.

Amongst NMDA antagonists, low perioperative doses of **ketamine** provide effective pain prevention, showing a good safety and tolerance profile; however, continuous monitoring and meticulous post-operative surveillance are necessary.

Clonidine was demonstrated to have opioid sparing effects; however, its side effects, such as bradycardia and hypotension, limit its use to the selected patients and necessitate widened monitoring and strict post-operative surveillance.

Lidocaine is an amide local anaesthetic characterised by antinociceptive, antiarrhythmic, anticoagulant, anti-inflammatory and wound healing properties. It deserves its place among adjuvants. The safety of perioperative lidocaine was demonstrated by the analysis of 16 randomised, double-blind placebo-controlled studies in which uniform dosing of lidocaine was used (30 min before surgery, 1.5 mg kg^{-1}; during the procedure, continuous infusion of 1.5–3 mg kg^{-1}; and post-operatively, 1–3 mg kg^{-1}). The findings revealed no severe side effects or complications associated with this therapy [59]. Contrary to the mechanism of action of opioids, the analgesic efficacy of lidocaine appears to be independent of physiological pain transmission pathways and effects on sodium channels. It is believed that this agent increases the intracellular concentration of calcium in sensory cortex neurons, which is likely to be responsible for the analgesic effect [60]. Clinical trials demonstrated the analgesic efficacy of lidocaine administered during the perioperative period and improved urinary bladder motor function after radical prostatectomy [61]; in abdominal surgeries (laparoscopies and laparotomies), significantly lower rates of atony and post-operative intestinal obstruction, nausea and vomiting were observed, which translated into shorter hospitalisations. The perioperative use of lidocaine reduces opioid requirements by 40% [62]. In addition to the analgesic effect, i.v. lidocaine inhibits the surgery-induced inflammatory reaction. Its post-operative use is believed to reduce plasma concentrations of IL-6, IL-8, C3a, IL-1ra, CD11b, L- and P-selectin [63]. Moreover, it is thought that the analgesic efficacy of lidocaine can be much higher for visceral pain than for somatic pain. Lidocaine owes its analgesic effect to the mechanism of antihyperalgesia rather than to direct analgesic action. The available studies that compared epidural analgesia with systemic lidocaine did not find a spectacular analgesic effect or reduced levels of proinflammatory cytokines and earlier return of motor function of the urinary bladder or intestines. However, considering the many contraindications for and complications with

epidural analgesia, systemic lidocaine can be a substitute for epidural anaesthesia, particularly in individuals undergoing abdominal surgeries [64, 65].

All of the studies devoted to the efficacy of lidocaine emphasise that the essence is its proper perioperative dosing (mentioned earlier) to achieve serum concentrations ranging from 1.1–4.2 μg mL^{-1} [63]. However, possible side effects should be borne in mind, and patients should be informed about them. The side effects include drowsiness, fatigue, nausea, lip numbness, a metallic taste in the mouth and dizziness [66].

Gabapentinoids are a unique group of drugs based on their mechanism of action: They bind with the alpha-2 delta subunit of the calcium channel in the central nervous system, which reduces the release of pronociceptive neurotransmitters. They are used as anticonvulsive agents and to manage neuropathic pain. Through numerous animal studies, however, their antinociceptive effects and efficacy in perioperative pain relief were demonstrated. Other researchers have suggested their sedative properties, which can be of additional benefit to patients who are experiencing pain. Compared with gabapentin, pregabalin is characterised by higher bioavailability after oral administration, higher specificity of action on calcium channels and lower incidences of adverse side effects. The clinical trials on acute pain showed the utility of these drugs for treating acute neuropathic pain, which allows for lower opioid doses, thus, decreasing the intensity of their side effects and leading to earlier ambulation after surgery and shorter hospitalisation. Long-term observations revealed lower percentages of chronic post-operative pain. The analysis of 18 prospective, randomised and blinded studies regarding the perioperative use of pregabalin for acute pain therapy demonstrated that although pregabalin increased the risk of dizziness and visual disorders, it significantly reduced the incidence of nausea and vomiting after surgery. Its side effects, such as drowsiness, sedation, visual disorders, and disorders of ventilation in the form of shallow and slowed down breathing, were more common in elderly patients and in those with sleep apnoea or kidney dysfunction. Based on the newest evidence, it should be highlighted that the balance of benefits to side effects in the case of pregabalin favours only some patients who are individually selected for surgical procedures. Further studies are being carried out, and their findings will create the basis for future guidelines [67].

Gabapentin in post-operative monoanalgesia (600 mg 4 h preoperatively and 24 h post-operatively) induces a comparable pain-relieving effect after laparotomy as when it is combined with ketamine and local anaesthesia [68]. A meta-analysis of available clinical studies conducted in 2014 disclosed that pregabalin showed significant analgesic effects and provided effective pain control after gynaecological procedures, contributing to a decrease in opioid requirements and thus reducing the side effects associated with their use [69, 70].

The final goals of acute pain therapy are based on the evidence for the analgesic efficacy of various groups of drugs characterised by good safety and tolerance profiles; their use is to limit the adverse side effects of opioids and to prevent the development of chronic pain. Considering the above, systemic ketamine, magnesium, gabapentinoids, clonidine or lidocaine can significantly increase the analgesic effects of the recognised analgesics used in monotherapy. The studies mentioned earlier demonstrate both the benefits of adjuvants and broadened indications for their administration. Moreover, there is consensus that ketamine, lidocaine, magnesium and gabapentinoids inhibit central sensitisation and can be used as components of preventive and pre-emptive analgesia [71].

Further prospective, randomised studies are required, particularly in elderly patients, children, patients with sleep apnoea and those with a tolerance to opioids.

The above guidelines for post-operative pain management will be shortly broadened to include recommendations regarding acute pain (unrelated to surgery) and post-traumatic pain management.

PAIN RELIEF IN ADULTS ACCORDING TO THE EXTENT OF SURGICAL TRAUMA

SURGICAL PROCEDURES ASSOCIATED WITH SLIGHT TISSUE DAMAGE

Procedures of small extent and post-operative pain intensity < 4 points according to NRS or VAS.

PHARMACOTHERAPY BEFORE SURGERY (PREVENTIVE ANALGESIA)

Alternatives:

— metamizole (1–2.5 g), intravenous or oral,
— paracetamol (1.0–2.0 g), intravenous or oral ,
— ketoprofen (50–100 mg), intravenous or oral,
— ibuprofen (200–400 mg), oral,
— diclofenac (50–100 mg), oral,
— other NSAIDs (oral).

PHARMACOTHERAPY AFTER SURGERY:

— metamizole (1 g–2.5 g, max. 5 g day^{-1}), intravenous or oral every 6–12 hours
— and/or paracetamol 1.0 g, intravenous or oral, every 6 h (max. 4 g $doba^{-1}$) combined with a non-selective NSAID in a continuous infusion or orally or a selective COX-2 inhibitor, oral

Later (post-operative day 1) oral analgesics can be used in fractionated doses:

— metamizole 500 mg, and/or,

— paracetamol (0.5–1 g) combined (or otherwise) with a non-selective or selective NSAID,
— ketoprofen (50 mg) p.o., every 6–8 h or,
— dexketoprofen (25 mg) p.o., every 6–8 h or,
— diclofenac (50 mg) p.o., every 8 h or,
— ibuprofen (400 mg) p.o., every 8 h or,
— naproxen (250–500 mg) p.o., every 8 h or,
— nimesulide (100 mg) p.o., every 12–24 h or,
— meloxicam (7.5 mg–15 mg) p.o., every 24 h.

Moreover, to facilitate post-operative analgesia in patients undergoing day case surgeries, it is suggested to provide patients with "pre-packaged take-home drugs" on discharge, that is, appropriate analgesics in suitable amounts (for the period of 3–7 days) and, e.g., antiemetic drugs (when opioids are used) specific to the type of surgery. For instance, for individuals with mild post-operative pain, below 4 according to NRS, the pre-packaged take-home analgesics should include:

— paracetamol (40 tablets 0.5 g); dosage 0.5–1 g every 6 h for 4–5 days
— and NSAIDs, e.g.:
  - ketoprofen (20 tablets 50 mg); 1 tablet every 6 h for 4–5 days or,
  - dexketoprofen (15 tablets 25 mg); 1 tablet every 8–12 h for 4–5 days or,
  - diclofenac (15 tablets 50 mg); 1 tablet every 8 h for 4–5 days or,
  - ibuprofen (15 tablets 400 mg); 1 tablet every 8 h for 4–5 days or,
  - naproxen (15 tablets 500 mg); 1 tablet every 8 h for 4–5 days or,
  - nimesulide, granules for suspensions, 100 mg, 9 sachets, 1 sachet every 12 h for 2–3 days or,
  - meloxicam tablets, 15 mg, 10 tablets, 1 tablet every 24 h for 2–3 days.

LOCAL ANALGESIA

Before surgery, the anticipated incision line should be injected with 10–20 mL lidocaine 1%, or 5–10 mL bupivacaine 0.25–0.125%, or 5–10 mL ropivacaine 0.2%, to induce the effect of pre-emptive analgesia; after completion of the surgery, depending on its type, re-injection of the wound; or a continuous infusion of LA through the catheter implanted in the surgical wound (an automated syringe or elastomeric pump);

SURGICAL PROCEDURES ASSOCIATED WITH MODERATE TISSUE DAMAGE

These include: abdominal surgical procedures with intact alimentary continuity that do not require opening the peritoneal cavity (cholecystectomy, nephrectomy, adrenalectomy), and orthopaedic surgeries, except for pelvic and thoracic, as well as reconstructions of large joints and gynaecological, urological and neurosurgical procedures. NSR or VAS post-operative pain intensity levels > 4 and post-operative pain persists for 3 days.

PHARMACOTHERAPY BEFORE SURGERY

Same procedures as for those with only slight tissue damage. Additionally, the following drugs, selectively or combined:

— clonidine tablets 75–150 µg, 1 h before surgery or as a slow intravenous infusion, 150 µg directly before the induction of anaesthesia,
— dexmedetomidine 200 µg, a slow intravenous infusion directly before induction of anaesthesia and/or,
— gabapentin, oral, 600 mg 4 h before surgery or pregabalin, oral, 50–75 mg 1 h before surgery and/or,
— lidocaine 1.5 mg kg^{-1}, a slow intravenous infusion before the induction of general anaesthesia and/or,
— ketamine 50 mg i.v. bolus before induction of general anaesthesia.

INTRAOPERATIVELY:

Lidocaine 1.5–3 mg kg^{-1} h^{-1}.

PHARMACOTHERAPY AFTER SURGERY:

— metamizole (1–2.5 g, max. 5 g day^{-1}) every 6–12 h, intravenous, and/or,
— paracetamol 0.5–1.0 g, intravenous, every 6 h combined (or otherwise) with ketoprofen (50 –100 mg) in an intravenous infusion every 12 h or dexketoprofen (50 mg) in an intravenous infusion every 8 h, and/or,
— lidocaine 0.5–1 mg kg^{-1} h^{-1}.

Additionally, in the case of pain, on demand — small doses of i.v. opioids using nurse-controlled analgesia (NCA; lockout interval 10 min):

— tramadol (10–20 mg) or,
— nalbuphine (10 mg) or,
— morphine (1–2 mg) or,
— oxycodone (1–2 mg).

When ineffective, PCA is recommended in the form of intravenous opioid supply:

— oxycodone, bolus 0.03 mg kg^{-1}, lockout interval 5–10 min, and/or,
— morphine, bolus 0.5–2.5 mg, lockout interval 5–15 min and/or,
— fentanyl, bolus 20–50 µg, lockout interval 5–10 min, and/or,
— sufentanil, bolus 4 µg, lockout interval 10 min, or,
— nalbuphine, bolus 1–3 mg, lockout interval 6–10 min, or,
— tramadol, bolus 10–25 mg, lockout interval 5–10 min*

*Oxycodone can be combined with morphine or fentanyl, or sufentanil.

Beginning on post-operative day 2, oral analgesics can be administered (unless contraindicated) in the following fractionated doses:

NON-OPIOIDS:
— metamizole 500 mg (max. 5 g day^{-1}), and/or,
— paracetamol 500 mg (max. 4 g day^{-1}),
— with (or without) NSAID:
  - diclofenac 50 mg (max. 200 mg day^{-1}), or,
  - ketoprofen 50 mg (max. 200 mg day^{-1}) or,
  - dexketoprofen 50 mg (max. 75 mg day^{-1}), or,
  - naproxen 250–500 mg (max. 1250 mg day^{-1}), or,
  - nimesulide, 100 mg (max. 200 mg day^{-1}) and/or,
  - meloxicam 15 mg (max. 15 mg day^{-1}).

OPIOIDS:
— tramadol 5–20 drops every 6–8 h (max. 400 mg day^{-1}) or,
— oxycodone 10–20 mg, controlled-release tablets (max. 10–20 mg every 12 h) or,
— buprenorphine 0.2–0.4 mg every 6–8 h (max. 2.4 mg day^{-1}).

In the case of nausea and/or vomiting: metoclopramide (p.o.), 10 mg every 6–8 h and/or ondansetron (p.o.), 4 mg every 8–12 h.

Caution! Metoclopramide and ondansetron should not used in patients who are receiving tramadol. In the case of nausea and vomiting in patients who have been administered tramadol, small doses of levomepromazine can be given as an antiemetic (12.5–50 mg, intravenous).

LOCAL ANALGESIA:

Before surgery (for pre-emptive analgesia), the anticipated incision line can be injected with:
— lidocaine 1%, 10–20 mL (when an intravenous infusion is used, the total lidocaine dose should be verified) or,
— bupivacaine 0.25–0.125%, 5–10 mL or,
— ropivacaine 0.2%, 5–10 mL.

After the completion of surgery and depending on type: the wound margins should be injected with LA solution (drugs and doses as above) or there should be a continuous infusion of LA through the indwelling catheter (Dosage Table 1):
— to the surgical wound,
— into the region of peripheral nerves,
— into the region of plexuses,
— to the paravertebral space,
— to the pleural cavity.

SURGICAL PROCEDURES ASSOCIATED WITH SUBSTANTIAL OR EXTENSIVE TISSUE DAMAGE

Abdominal surgical procedures that require opening the peritoneal cavity, procedures within the pelvis and spinal cord, large joint reconstruction, cardiac and thoracic surgeries and those involving more than one body cavity (thorax, abdomen, pelvis). NRS or VAS anticipated post-operative pain intensity levels > 6 and duration of post-operative pain longer than 5 days. As a rule, multimodal analgesia should be applied, verified with the degree of pain intensity measured regularly using the scale chosen. When choosing the ingredients of multimodal analgesia, the following should be considered: lack of contraindications for each of the drugs, appropriate dosing and the fact that in the case of some drugs recommended in the current guideline, their summaries of product characteristics (SPCs) do not include indications for post-operative pain therapy.

PHARMACOTHERAPY BEFORE SURGERY (PREVENTIVE ANALGESIA)
— metamizole (1–2.5 g), intravenous or oral,
— paracetamol (1.0–2.0 g), intravenous or oral,
— ketoprofen (50–100 mg), intravenous or oral,
— ibuprofen (200–400 mg), oral,
— diclofenac (50–100 mg), oral
— other NSAIDs, oral.

Additionally, the following drugs, selectively or combined:
— clonidine tablets 75–150 µg 1 h before surgery or as a slow intravenous infusion 150 µg directly before the induction of anaesthesia or,
— dexmedetomidine 200 µg, a slow intravenous infusion directly before the induction of general anaesthesia,
— gabapentin, oral 600 mg 4 h before surgery or,
— pregabalin, oral 50–75 mg h^{-1} before surgery,
— lidocaine 1.5 mg kg^{-1} body weight, a slow intravenous infusion before the induction of general anaesthesia,
— ketamine 50 mg, intravenous bolus before the induction of general anaesthesia.

INTRAOPERATIVELY

Lidocaine 1.5–3 mg kg^{-1} h^{-1}.

PHARMACOTHERAPY AFTER SURGERY:
— metamizole (1 –2.5 g, max. 5 g day^{-1}), intravenous, every 6–12 h; and/or,
— paracetamol 0.5–1.0 g, intravenous, every 6 h combined (or otherwise) with ketoprofen (50–100 mg), an intravenous infusion every 12 h or,
— dexketoprofen (25 mg), an intravenous infusion every 8 h.
— lidocaine, an intravenous infusion 0.5-1 mg kg^{-1} h^{-1},
— a continuous infusion of an opioid (e.g., morphine, oxycodone, fentanyl, sufentanil, nalbuphine) in a dose determined by titration:

- morphine, a single intravenous bolus 2.5–10 mg; the dose can be repeated after 4–6 h or a continuous infusion 0.8–2.5 mg h^{-1} or PCA, bolus dose 0.5–2.5 mg, lockout interval 5–15 min,
- oxycodone, a single intravenous bolus, 1–10 mg for 1–2 min; the dose can be repeated after 4 h or a continuous infusion, 2 mg h^{-1} or PCA, bolus dose 0.03 mg kg^{-1}, lockout interval 5–10 min,
- fentanyl, single bolus 50–200 μg; a dose of 50 μg can be repeated after 20–40 min or a continuous infusion, 0.05–0.08 μg kg^{-1} min^{-1} or PCA, bolus dose 20–50 μg, lockout interval 5–10 min,
- sufentanil, a single bolus 0.3 μg kg^{-1} or a continuous infusion 0.1 mg kg^{-1} h^{-1} PCA–bolus dose 4 μg, lockout interval 10 min,
- nalbuphine, a single intravenous bolus 0.1–0.3 mg kg^{-1} (max. 20 mg); the dose can be repeated after 3–6 h or a continuous infusion 0.04–0.32 mg kg^{-1} h^{-1} or PCA, bolus dose 1–3 mg, lockout interval 6–10 min

It should be remembered to relieve any shooting pains using the additional doses of opioids:

— morphine 1–2 mg i.v., can be repeated after 10–15 min,
— oxycodone 1–2 mg i.v., can be repeated after 15 min.

During the next post-operative days, the analgesic management provided should be modified based on the level of pain intensity determined using the chosen scale.

Except for procedures that require opening the pleural cavity and disrupting the continuity of the gastrointestinal tract, the enteral (oral) route of analgesic administration should be considered.

NON-OPIOIDS:

— metamizole 500 mg (max. 5 g day^{-1}) and/or,
— paracetamol 500 mg (max. 4 g day^{-1}),
— together (or otherwise) with NSAID,
— diclofenac 50 mg (max. 200 mg day^{-1}), or,
— ketoprofen 50 mg (max. 200 g day^{-1}) or,
— dexketoprofen 25 mg (max. 75 g day^{-1}), or,
— naproxen 250–500 mg (max. 1250 mg day^{-1}), or,
— nimesulide 100 mg (max. 200 mg day^{-1}) or,
— meloxicam 15 mg (max. 15 mg day^{-1}).

OPIOIDS:

— tramadol 5–20 drops every 6–8 h (max. 400 mg day^{-1}) or,
— oxycodone 20–40 mg, controlled-release tablets (max. 20–40 mg every 12 h) or,
— buprenorphine 0.2–0.4 mg (s.l.) every 6–8 h (max. 2.4 mg day^{-1}).

In cases of nausea and/or vomiting: metoclopramide (p.o.) 10 mg every 6–8 h and/or ondansetron (p.o.) 4 mg every 8–12 h.

Caution! Metoclopramide and ondansetron should not be used in patients who are receiving tramadol. In the case of nausea and vomiting in patients who are being treated with tramadol, small doses of levomepromazine as an antiemetic can be administered (12.5–50 mg i.v.)

LOCAL ANALGESIA

In the majority of cases in this group of procedures, regional analgesia is a continuation of surgical anaesthesia. Continuous epidural analgesia, together with PCEA using LAs and opioids, is currently recommended only for select procedures (Table 2).

OTHER CONTINUOUS REGIONAL TECHNIQUES

— subarachnoid (isobaric ropivacaine 0.2%, initial dose 1 mL h^{-1}, bolus dose 0.5 mL, lockout interval 30 min); morphine 0.25–1 mg, only single doses (peak action after 20–60 min, duration of analgesic action 8–12 h),
— paravertebral (dosage in Table 2),
— transverse abdominis plane (TAP) block (6–8 mL h^{-1} $side^{-1}$ ropivacaine 0.2%),
— peripheral blocks (dosage in Table 2).

POST-OPERATIVE PAIN RELIEF IN CHILDREN

Post-operative pain management is one of the crucial elements of caring for children who undergo surgical procedures. The guidelines for analgesic management presented below include principles based on evaluation of the patient's condition as well as the type and extent of the surgery. Because of the highly diverse ages of potential patients, concomitant diseases and the extent of surgery, it is difficult to establish unified pain management practices. The guidelines presented are based on available clinical essential evidence, including evidence-based medicine (EBM) assumptions. They were established based on literature data, including the Australian & New Zealand College of Anaesthetists (ANZCA) guidelines of 2010 and the American Psychological Association (APA) guidelines of 2012.

A vital nociception-related element in newborns is the impact of long-term pain stimulation in the early period of life on the remote consequences of untreated pain. Long-term pain stimulation in newborns results not only in an increase in the somatosensory area of cerebral cortex that is responsible for pain perception but also in more complex changes involving the development of hypoal-

Table 2. Continuous peripheral nerve blocks in the perioperative period-indications, methods, dosages

Surgery/trauma	Continuous block	Infusion recommended
Total or partial shoulder arthroplasty, rotator cuff repair, "frozen" (painful) shoulder, biceps surgery, proximal humerus fracture	Brachial plexus, interscalene approach	Initial bolus: 20 mL ropivacaine 0.5% or bupivacaine0.375%, continuation of infusion: 5–10 mL h^{-1} ropivacaine 0.1–0.3% or bupivacaine 0.125–0.25%
Distal humerus fracture, elbow arthroplasty, radial fracture and surgery, ulnar fracture and surgery, wrist arthrodesis, re-implantation surgery, extensive upper limb trauma	Brachial plexus, supra- or subclavicular, axillary approach	Initial bolus: 20 mL ropivacaine 0.5% or ropivacaine 0.375%, continuation of infusion: 5–10 mL h^{-1} of ropivacaine 0.1–0.3% or bupivacaine 0.125–0.25%
Unilateral: thoracotomy, extensive breast surgery (T 4–5), rib fracture, nephrectomy (T 7). Bilateral: laparotomy (T 8), bladder resection (T 10)	Paravertebral block in the thoracic segment	Initial bolus: 15 mL ropivacaine 0.5% through the catheter or bupivacaine 0.375%, continuation of infusion: 5–10 mL h^{-1} of ropivacaine 0.1–0.3% or bupivacaine 0.125–0.25% through the catheter
Primary hip arthroplasty, revision of hip arthroplasty, femoral fractures	Lumbar plexus block	Initial bolus: 20 mL ropivacaine 0.2–0.5%; or bupivacaine 0.25–0.375%, continuation of infusion: 5–10 mL h^{-1} ropivacaine 0.1–0.3%; or bupivacaine 0.125–0.25%
Femoral fractures, anterior cruciate ligament reconstruction, total knee arthroplasty, patella repair, passive and active rehabilitation of the knee joint	Femoral nerve block	Initial bolus: 20 mL ropivacaine 0.2–0.5%; or bupivacaine 0.25–0.375%, continuation of infusion: 5–10 mL h^{-1} ropivacaine 0.1–0.3% or bupivacaine 0.125–0.25%
Knee arthroplasty, posterior cruciate ligament reconstruction	Femoral and sciatic nerve block (transsacral, gluteal or subgluteal approach)	Initial bolus (once foot dorsiflexion reflex has been checked): 6–12 mL ropivacaine 0.2%; or bupivacaine 0.125%, continuation of infusion: 3–8 mL h^{-1} ropivacaine 0.1–0.2% or bupivacaine 0.125%
Fractures and surgery of the tibia and fibula, talus and talocalcaneal anastomosis, hallux valgus repair	Sciatic nerve block (anterior, gluteal, subgluteal or lateral popliteal approach)	Initial bolus (one active dorsiflexion reflex has been checked): 5–10 mL ropivacaine 0.2–0.5%; continuation of infusion: 5–10 mL h^{-1} ropivacaine 0.1–0.2% or bupivacaine 0.125%
Talus anastomosis, total ankle arthroplasty	Femoral or tibial and sciatic nerve block	Initial bolus: 20 mL ropivacaine 0.2%; or bupivacaine 0.125%, continuation of infusion: 5–10 mL h^{-1} ropivacaine 0.1% or bupivacaine 0.0625%

Table 3. Epidural analgesia — recommended drugs and doses

Procedure	Location	Initial dose	Continuous analgesia
Lower limbs	L 2-L 3; L 3-L 4	1–2 mL per segment	bupivacaine 0.125% or ropivacaine 0.2% + fentanyl 2 μg mL^{-1} or sufentanil 0.5–1 μg mL^{-1} flow: 4–8 mL h^{-1}
Abdominal and pelvic surgery	T 8-T 10	Titration 5 mL every 10 min	
Thoracic and epigastric surgery	Centre of surgical incision T 4-T 8	0.5 mL per segment Saturating dose 5 mL every 10 min	

gesia to thermal stimuli together with hyperalgesia in the inflammatory regions. For many years, the view that children do not feel pain or do not remember the experiences associated with it lingered among many physicians and in various circles. Moreover, insufficient knowledge about pain management, fears of adverse side effects of opioids and lack of analgesic management standards resulted in ineffective pain treatment in children.

Tabela 4. Zastosowanie mieszaniny leków znieczulających miejscowo i opioidu w zewnątrzoponowej analgezji pooperacyjnej

Procedures Place of epidural catheter implantation	Continuous infusion into the epidural space
Thoracotomy T 5-T 6 Th 6-T 7 T 7-T 8	bupivacaine 0.1–0.25% + adrenalin 2 μg mL^{-1} ropivacaine 0.2% + adrenalin 2 μg mL^{-1} combined with fentanyl, bolus 50-100 μg, 0.1–0.2 mL h^{-1} (2–5 μg mL^{-1}) or sufentanil, bolus 20–30 μg, 0.1–0.2 mL h^{-1} (0.5–2 μg mL^{-1})
Epigastric and intragastric surgery T 10-T 11 T 12-L 1	bupivacaine 0.1–0.25% + adrenalin 2 μg mL^{-1} ropivacaine 0.2%+ adrenalin 2 μg mL^{-1} combined with fentanyl, bolus 50–100 μg, 0.1–0.2 mL h^{-1} (2–5 μg mL^{-1}) or sufentanil, bolus 20–30 μg, 0.1–0.2 mL h^{-1} (0.5–2 μg mL^{-1})
Hypogastric and lower limb surgery L2-L3 L3-L4	bupivacaine 0.1–0.25% + adrenalin 2 μg mL^{-1} ropivacaine 0.2%+ adrenalin 2 μg mL^{-1} + fentanyl, bolus 50–100 μg, 0.1–0.2 mL h^{-1} (5 μg mL^{-1}) or sufentanil, bolus 20–30 μg, 0.1–0.2 mL h^{-1} (1–2 μg mL^{-1}) or morphine, bolus 2–4 mg, 8–15 mL h^{-1} (0.05 mg mL^{-1})

The first sensory receptors in children are already developed after week 7 of foetal life. At gestational week 20, the receptors cover the entire skin and mucosa surface. Simultaneously, synaptic structures mature in the posterior horn of the spinal cord to become fully mature during gestational week 30. Complete myelinisation of the nerve fibres that conduct pain is achieved at foetal week 37. The development of cerebral hemispheres begins in gestational week 8; by week 20, each foetus has the full complement of nervous cells. Apart from the structural and functional maturity of that conduction pathways, an important role is played by the neurotransmitters that are released and by the endogenous opioid system. The concentration of substance P in the nervous cells and the number of CNS receptors specific to it are higher in children than in adults. During gestational week 20, the pituitary cells begin to produce endorphins. After delivery, newborns have a five-fold higher concentration of endorphins compared with adults.

EVALUATION AND MEASUREMENT OF PAIN INTENSITY IN CHILDREN

Proper evaluation of pain in children is a prerequisite for adequate analgesic management. With proper evaluation, patients are appropriately treated, their physical and mental comfort are improved, the risk of complications is reduced and convalescence time is shortened, resulting in reduced hospitalisation and better outcomes. Unfortunately, there are no universal tools for pain evaluation that can be used in all age groups. This particularly concerns newborns and preverbal children but also children with psychomotor impairments and children in all age groups who have been intubated. The majority of guidelines recommend the use of pain intensity evaluation scales (physiological and/or behavioural parameters are taken into consideration) suitable for the patient's age and clinical condition. Self-report tools are most commonly used in children, e.g., FACES (Wong-Baker), the Numerical Rating Scale (NRS), the visual analogue scale (VAS) and those based on behaviour or behaviour and parameters, e.g., CRIES, COMFORT, PIPP, FLACC, CRIES, CHEOPS (tab. 5, 6).

THE ANZCA 2010 RECOMMENDATIONS [89] WITH MODIFICATIONS

Newborns:
- acute and post-operative pain: PIPP, NFCS, CRIES,
- intensive care: COMFORT.

Infants and small children:
- acute and post-operative pain: FLACC, CHEOPS, PPPM,
- intensive care: COMFORT.

Children aged 4–12 years:
- acute and post-operative pain: FACES Pain Score-Revised, NRS, VAS,
- intensive care: COMFORT.

APA RECOMMENDATIONS [90]:

- newborns–children < 3 years of age: COMFORT, FLACC,
- children aged 4 years: FPS-R + COMFORT, FLACC,
- children aged 5–7 years: FPS-R,
- children above the age of 7 years: VAS, NRS, FPS-R.

Table 5. Self-report tools [72–74]

Procedure-related pain	Post-operative pain	Disease-related pain
FACES (Wong-Baker)	FACES (Wong-Baker)	FACES (Wong-Baker) 3–18 years of age
3–18 years of age	3–18 years of age	Faces Pain Score-Revised 4–12 years of age
Faces Pain Score-Revised	Faces Pain Score-Revised	VAS i NRS
4–12 years of age	4–12 years of age	≥ 8 years of age
VAS I NRS	≥ 8 years of age	
≥ 8 years of age	Pieces of Hurt Tool	
Pieces of Hurt Tool	3–8 years of age	
3–8 years of age		
MSPCT		
4–6 years of age		

VAS — Visual Analogue Scale; NRS — Numerical Rating Scale; MSPCT — The Multiple Size Poker Chip Tool

Table 6. Scales based on behaviour or behaviour and physiological parameters [75–88]

	Procedure-related pain	Post-operative pain	Intensive care
Premature babies and newborns	PIPP NFCS	PIPP CRIES COMFORT	COMFORT
Children and young individuals without cognitive disorders	FLACC 1–18 years of age	FLACC 1–18 years of age PPPM	COMFORT
	CHEOPS 1–18 years of age		
Children and young individuals with cognitive disorders	NCCPC-R 3–18 years of age	NCCPC-PV 3–18 years of age	COMFORT
	PPP 1–18 years of age	PPP 1–18 years of age FLACC-Revised 4–18 years of age	

PIPP — Premature Infant Pain Profile; NFCS — Neonatal Facial Coding Scale; FLACC — Face, Legs, Arms, Cry, and Consolability; CHEOPS — Children's Hospital of Eastern Ontario Pain Scale; PPPM — Parents Postoperative Pain Measure; NCCPC-R — Non-Communicating Children's Pain Checklist; PPP — The Pediatric Pain Profile; NCCPC-PV — Non-Communicating Children's Pain Checklist-Postoperative Version

The disadvantage of all the above scales is that they rely on the subjectivity and relativism of the rater's evaluation [92]. The results of recent studies suggest the possibility of objectively evaluating pain intensity (pain stress) using the skin conductance algesimeter (SCA) to measure the sympathetic system stimulation caused by a pain stimulus. The activation of sympathetic fibres that innervate sweat glands induces the release of their contents (so-called emotional sweating), reduces resistance and increases skin conductance. Quick absorption of the released sweat re-decreases skin conductance. Pain stimuli induce a rapid increase in emotional sweating and oscillations of skin conductance. When a pain stimulus ceases to act, skin conductance immediately reduces. The changes are recorded by the electrodes located on the plantar surface, which is rich in sweat glands in newborns and infants. The resultant conductance oscillations reach the central unit, where they are analysed following conversion. The software-converted signal is expressed in the form of oscillation/sec.index, which corresponds to the intensity of pain stress (Table 7) [93].

ACUTE PAIN ALLEVIATION IN CHILDREN ACCORDING TO THE EXTENT OF SURGICAL TRAUMA

SURGICAL PROCEDURES ASSOCIATED WITH SLIGHT TISSUE DAMAGE (DAY CASE PROCEDURES)

NRS or VAS post-operative pain intensity < 4.

PREOPERATIVE PHARMACOTHERAPY

— PRE-EMPTIVE ANALGESIA (FIG. 1)

EMLA cream — used in children > 2 years of age in whom any vein can be found and the time of anaesthesia initiation can be approximately determined. The cream is not applied on children who cannot have contact, who have i.v. lines, ports or vascular catheters, and whose veins cannot be found. Dosage: 2 g per 20 cm^2 skin, cover with an occlusive dressing for 1–2 h.

Table 7. Measurement of skin conductance oscillations using the SCA

White: 0.00–0.07 impuls s^{-1}	A quiet newborn
Bright yellow: 0.14 impuls s^{-1}	A quiet newborn, slight motor activity
Yellow: 0.21–0.27 impuls s^{-1}	An active newborn, possible discomfort experienced
Orange: 0.33 impuls s^{-1}	A newborn is likely to feel pain/discomfort, assess the situation
Red: 0.40–0.70 impuls s^{-1}	A newborn is most likely to feel pain/discomfort

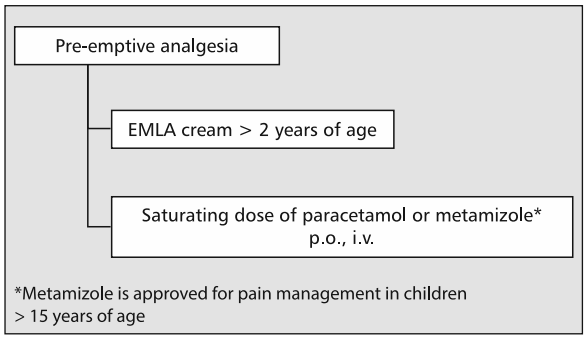

Figure 1. Preoperative pharmacotherapy associated with Surgical procedures with slight tissue damage — pre-emptive analgesia

POST-OPERATIVE PHARMACOTHERAPY

— LOCAL ANALGESIA (FIG. 2)

Before surgery, the anticipated incision line should be injected with lidocaine 1% or bupivacaine 0.25–0.5% (5–10 mL) as pre-emptive analgesia unless block anaesthesia is administered.

After the completion of surgery, re-injecting the wound depending on the type of procedure.

Intra-articular administration of LA 5–10 mL bupivacaine 0.25–0.5% and/or opioid: morphine 1–2 mg or fentanyl 20–25 mg.

SURGICAL PROCEDURES ASSOCIATED WITH MODERATE TISSUE DAMAGE

NRS or VAS post-operative pain intensity levels 4–6 and post-operative pain duration usually shorter than 3 days.

PHARMACOTHERAPY BEFORE SURGERY

Same as for surgical procedures associated with slight tissue damage.

PHARMACOTHERAPY AFTER SURGERY (FIG. 3)

On days 2–3, analgesics can be administered in fractionated doses orally or rectally.

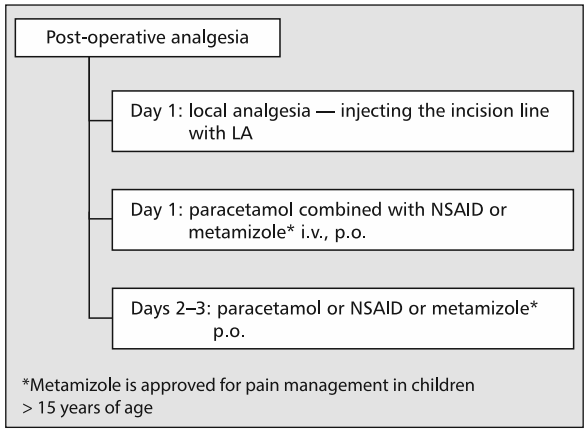

Figure 2. Post-operative pharmacotherapy associated with Surgical procedures with slight tissue damage

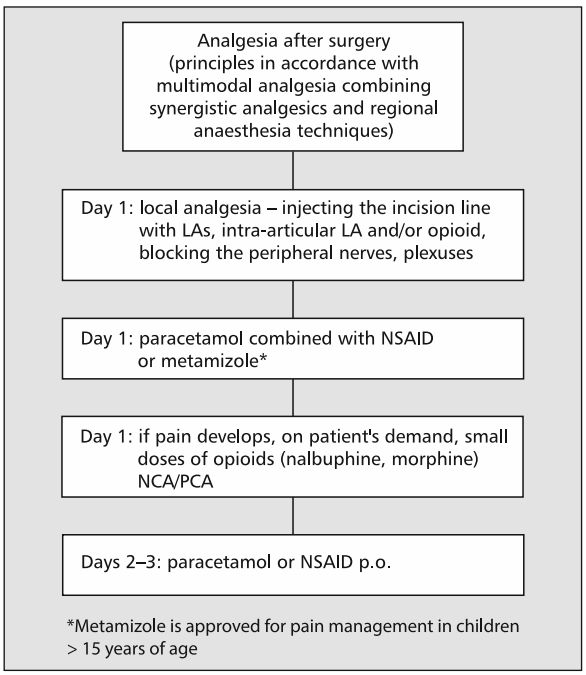

Figure 3. Post-operative pharmacotherapy associated with surgical procedures with moderate tissue damage

Additionally, if pain develops, on patient's demand, small doses of opioids should be administered using the NCA method or PCA with opioids, when available.

Continuous monitoring of basic vital parameters, e.g., pulse, respiratory rate, pain intensity, depth of sedation, adverse side effects, is absolutely obligatory!!!

ANTIEMETIC DRUGS

Metoclopramide — i.v. 0.1 mg kg^{-1} every 6–8 h up to 5 mg; metoclopramide cannot be used in patients who are receiving tramadol.

Ondansetron — i.v. 0.05–0.1 mg kg^{-1} every 8–12 h up to 4 mg; ondansetron cannot be used in patients who are receiving tramadol.

Dexamethasone — i.v. 0.15 mg kg^{-1} every 8–12 h up to 5 mg.

LOCAL ANALGESIA

Before surgery, injecting the incision line with a solution of 1% lidocaine or 0.25–0.5% bupivacaine (5–10 mL) as pre-emptive analgesia unless block anaesthesia is administered.

After surgery, depending on type, re-injecting the wound.

Intra-articular administration of LA 5–10 mL 0.25–05% bupivacaine and/or opioid: morphine 1–2 mg or fentanyl 20–25 mg.

SURGICAL PROCEDURES ASSOCIATED WITH SUBSTANTIAL TISSUE DAMAGE

NRS or VAS post-operative pain intensity levels > 7 and post-operative pain duration longer than 3 days.

PHARMACOTHERAPY BEFORE SURGERY

Same as for surgical procedures associated with slight tissue damage.

PHARMACOTHERAPY AFTER SURGERY

Continuous opioid infusion (see Fig. 4): morphine, nalbuphine.

Drug administration in this form only in paediatric intensive care units (PICUs).

If available, PCA with opioids can be used.

If appropriate infusion pumps are not available, the above-mentioned drugs can be used in fractionated doses combined with i.v. infusion of paracetamol.

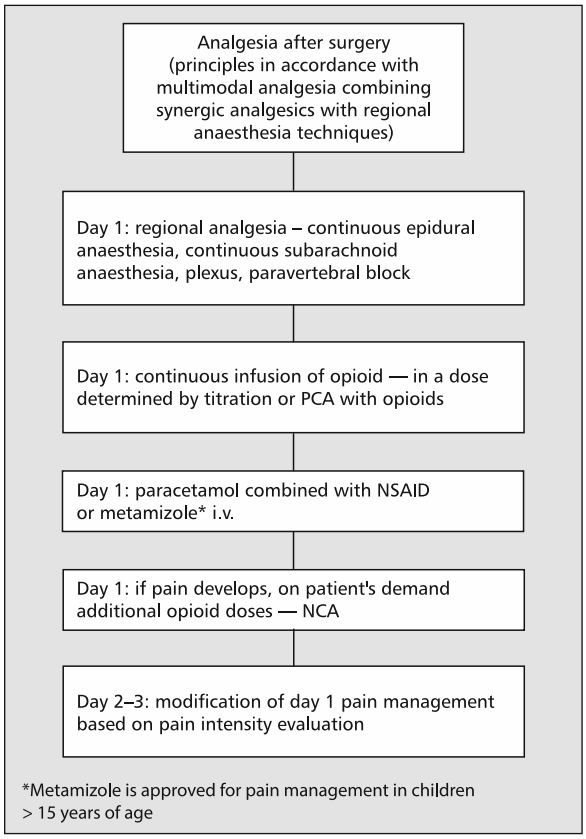

Figure 4. Post-operative pharmacotherapy associated with surgical procedures with substantial tissue damage

ANTIEMETIC DRUGS

Metoclopramide i.v. — 0.1 mg kg^{-1} every 6–8 h up to the dose of 5 mg; metoclopramide cannot be used in patients who are receiving tramadol.

Table 8. Analgesic dosages of paracetamol for children [93–95]

Age	Administration route	Saturating dose (mg kg^{-1})	Maintenance dose (mg kg^{-1})	Interval between doses (h)	Max. daily dose (mg kg^{-1})	Duration of max. daily dose administration (h)
28–32 weeks	oral	20	10–15	8–12	30	48
	rectal	20	15	12	30	48
33–52 weeks	oral	20	10–15	6–8	60	48
	rectal	30	20	8	60	48
> 3 months	oral	20–30	15	4–6	90	48–72
	rectal	30–40	15–20	6–8	90	
Body weight (kg)	**Administration route**	**Dose**	**Interval between doses (h)**		**Max. daily dose**	
< 5 (newborns)	i.v.	7.5 mg kg^{-1}	4–6		30 mg kg^{-1}	
5–10	i.v.	10 mg kg^{-1}	4–6		40 mg kg^{-1}	
10–50	i.v.	15 mg kg^{-1}	4–6		60 mg kg^{-1}	
> 50	i.v.	1.0 g	4–6		4.0–5.0 g	

Table 9. Analgesic dosages of metamizole for children [93–95]

Administration route	Dose	Interval between doses (h)	Max. daily dose	Comments
i.v. oral	10–15 mg kg^{-1} 5–20 mg kg^{-1}	6–8	60 mg kg^{-1}	approved > 15 years of age

Table 10. Analgesic dosages of non-steroidal anti-inflammatory drugs (NSAIDs) for children [93–95]

NSAID	Dose	Interval between doses (h)	Max. daily dose	Comments
Ibuprofen	5–10 mg kg^{-1} p.o./p.r.	6–8	30 mg kg^{-1}	Approved > 3 months of age
Ketoprofen	50–100 mg i.v. 1 mg kg^{-1}	6–8–12	200 mg 4 mg kg^{-1}	Approved > 15 years of age
Diclofenac	50–150 mg p.o./p.r. 1 mg kg^{-1}p.r.	8	150 mg 3 mg kg^{-1}	Approved > 14 years of age
Naproksen	7.5 mg kg^{-1}p.o./p.r.	12	15 mg kg^{-1}	Approved > 5 years of age
Dexketoprofen	25 mg i.v. 50 mg i.v.	8 h p.o. 6–8–12 i.v.	75 mg i.v. 150 mg i.v.	Approved in adult patients

Table 11. Analgesic dosages of opioids for children [93–95]

Opioid	Administration route	Dose	Interval between doses (h)	Infusion	Comments
Morphine	i.v./s.c.	Newborns 0.025 mg kg^{-1} Children 0.05-0.2 mg kg^{-1}	3–4	10–40 µg kg^{-1} h^{-1}	Preparation- 1 mg MF/kg/50 mL = 20 mg kg^{-1}g kg^{-1}mL^{-1} Bolus dose administered in a 30-minute infusion Obligatory monitoring of the patient
	p.o.	Newborns 0.08 mg kg^{-1} Children 0.2–0.5 mg kg^{-1}	4		
Fentanyl	i.v.	1–5 µg kg^{-1}		0.5–2.5 µg kg^{-1} h^{-1}	
Sufentanil	i.v.	0.05–0.5 µg kg^{-1}		0.05–1 µg kg^{-1} h^{-1}	
Tramadol	i.v.	1–2 mg kg^{-1}	4–6	0.07–0.25 mg kg^{-1} h^{-1}	Approved > 12 years of age
Oxycodone	i.v./p.o.	0.05–0.15 mg kg^{-1}	3–4		Approved > 12 years od age
Nalbuphine	i.v.	0.1–0.2 mg kg^{-1}	3–6	bolus 0.2 mg kg^{-1} infusion 0.1 mg kg^{-1}h^{-1}	Approved > 18 months

Table 12. Patient-controlled analgesia (PCA) [93–95]

Drug	Initial dose	Infusion	Bolus	Max. 4-hour dose	Duration of pump block
Morphine	50–100 µg kg^{-1}	0–4 µg kg^{-1} h^{-1}	10–20 µg kg^{-1}	300 µg kg^{-1}	10–15 min
Fentanyl	0,5–1 µg kg^{-1}	0.5–1 µg kg^{-1} h^{-1}	0.5–1 µg kg^{-1}	4–8 µg kg^{-1}	5–10 min
Oxycodone	0.03 µg kg^{-1}				5–10 min

Table 13. Nurse-controlled analgesia (NCA) [93–95]

Drug	Initial dose	Infusion	Bolus	Duration of pump block
Morphine	50–100 µg kg^{-1}	0–20 µg kg^{-1} h^{-1}	10–20 µg kg^{-1}	20–30 min

Ondansetron i.v. — 0.05–0.1 mg kg^{-1} every 8–12 h up to the dose of 4 mg; ondansetron cannot be used in patients who are receiving tramadol.

Dexamethasone i.v. — 0.15 mg kg^{-1} every 8–12 h up to the dose of 5 mg.

DRUG DOSAGES

The characteristics of, contraindications for and side effects of individual preparations should be carefully studied to ensure the safety of analgesics. Dosage should follow the manufacturer's recommendations. In special cases, the guidelines of scientific societies and literature data can be applied. Analgesic dosages for children are presented in Table 8–13 [93–95].

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