

Postoperative pain management — 2018 consensus statement of the Section of Regional Anaesthesia and Pain Therapy of the Polish Society of Anaesthesiology and Intensive Therapy, the Polish Society of Regional Anaesthesia and Pain Therapy, the Polish Association for the Study of Pain and the National Consultant in Anaesthesiology and Intensive Therapy

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INTRODUCTION

Over 230 million people worldwide undergo surgery each year, with this number increasing annually [1]. More than 80% of surgical patients experience acute postoperative pain, including about 75% who rate its intensity as moderate, severe or extreme. According to the available data, less than half of surgical patients report adequate postoperative pain relief.

Surgery-related trauma usually induces postoperative pain which should be alleviated as quickly and effectively as possible. According to statistics, clinical management of postoperative pain is far from being perfect, despite significant advancements in evidence-based knowledge [2–4].

Severe pain is associated with decreased patient satisfaction, delayed post-surgery ambulation, the development of chronic postoperative pain, increased incidence of severe complications (including pulmonary and cardiac) and higher postoperative morbidity and mortality [5–9]. Therefore, it is essential to properly identify the surgical procedures in-

ducing severe pain and to optimally tailor the strategy of postoperative analgesia to the patient's needs and surgical procedures [10].

German researchers [11] have put forward a hypothesis that a systematic and standardised comparison of pain following all surgeries can help to identify the procedures resulting in severe postoperative pain. The results of their study are surprising. In cases of extensive thoracic and abdominal surgeries, the NRS score was low (≤ 4). The percentage of advanced methods of analgesia, including block analgesia, used in such procedures was over 50%. Although the severity of pain following laparoscopic procedures was significantly higher, patients received relatively low doses of postoperative opioids or did not receive them at all (72%). The above results show that in many procedures, the extent of the incision and range of surgery-related trauma are not directly associated with the intensity of postoperative pain. According to the authors, the surgical procedures with poorly controlled postoperative pain include tonsillectomy,

haemorrhoidectomy with plastic reconstruction, appendectomy and laparotomy cholecystectomy.

Acute pain management is based on a proper assessment of its severity being performed several times a day, individual titration of analgesics and the minimisation of adverse effects. However, it has been demonstrated that in many cases the severity of pain is erroneously assessed by the medical personnel, which translates into improper titration and dosing of drugs and indirectly affects the percentage of adverse reactions associated with pain management [12].

The mechanisms of development of acute postoperative pain are more complex than earlier believed while adequate pain management requires much more than just opioids. Therefore, it is not surprising that there is a comprehensive scientific evidence base that provides guidelines for postoperative pain management. One of the documents available is the fourth edition of *Acute Pain Management: scientific evidence*, published by the Australian and New Zealand College of Anaesthetists [13]. The size of this guideline summary reflects the complexity of the issue being discussed. It contains 650 pages, assesses over 8,500 scientific reports and condenses an enormous amount of information into 669 key recommendations.

The assumption of the working group updating the Polish guidelines was to collect the scientific reports regarding acute postoperative pain that appeared after the publication of the previous edition of Polish guidelines for acute postoperative pain management (2014), in order to collate the European, American and New Zealand recommendations published since then and to prepare updated guidelines for postoperative pain management. Following the procedure-specific postoperative pain management (PROSPECT) assumptions, our management guidelines in the selected surgical procedures were formulated, albeit without categorisation of individual procedures. The authors of the present guidelines have divided the material into three major parts regarding the current state of knowledge on the drugs used for acute pain therapy, general recommendations for postoperative pain therapy.

The objective of this new version of the recommendations is also to draw attention to the fact that postoperative pain management is not merely a humanitarian task aimed at reducing patients' suffering and improving satisfaction with the treatment received, but also significantly reduces post-surgery morbidity and, most likely, post-surgery mortality. Moreover, early rehabilitation and shortened hospital stays are associated with economic benefits for health care institutions, which is also of considerable importance [14].

The literature material collected and used for preparation of the majority of the recommendations was classified according to grades of recommendation (Table 1) and levels of evidence (Table 2) [15].

OPIOIDS FOR POSTOPERATIVE PAIN RELIEF

Opioids are an important group of analgesics used for the management of acute and chronic pain syndromes. They are an effective tool in treating moderate and severe pain of various aetiologies, provided that their use is supported by good knowledge of their mechanisms of action, potential adverse effects they can induce, as well as interactions with other drugs simultaneously administered. Opioids act on three types of opioid receptors, namely MOR (mu), DOR (delta) and KOR (kappa). Opioid analgesics used in everyday clinical practice differ in their affinity to individual types of opioid receptors, interactions with these receptors (agonists, partial agonists, antagonists), strength of action, clinical efficacy and safety profiles. It is essential to know these differences in terms of the efficacy of individual opioids and the adverse reactions they can induce. Additionally, significant individual differences in responses to particular opioids are observed. Opioids affect the functioning of many systems and organs thus inducing specific clinical effects.

Table 1. Grades of recommendation

I — strongly recommended	Scientific data and generally accepted opinions prove that the therapeutic management is beneficial, useful and effective.
II	Scientific data and opinions regarding the usefulness and efficacy of therapeutic management are inconsistent
IIa — somewhat recommended	Scientific data and opinions speak in favour of usefulness and efficacy
IIb — may be considered	Usefulness or efficacy poorly confirmed by scientific data and opinions
III — strongly not recommended/ /definitely to be avoided	Scientific data demonstrate that therapeutic management is neither useful nor effective; in some cases can even be harmful

Table 2. Levels of evidence according to [15]

A	Data from numerous randomised controlled studies or meta-analyses
B	Data from one randomised controlled study or non-randomised studies
C	Data from small-sized studies, retrospective studies or registers

They exert analgesic effects, influence mood and behaviour and affect the functioning of the respiratory, cardiovascular, gastrointestinal, neuroendocrine and immune systems. It should be remembered that the majority of opioids cause immunosuppression, which can result in an increased risk of postoperative infections [16] and possible opioid-induced hyperalgesia (opioid paradox), manifesting itself as an increasingly severe pain despite opioid dose escalation [17]. An increasing number of studies in the literature demonstrate a higher probability of neoplastic disease progression in patients undergoing surgical oncological procedures being treated with opioids in the intra- and postoperative period, as compared with patients subjected to block anaesthesia [18]. However, the above data need to be confirmed by large population-based studies.

The most common adverse effects associated with opioid analgesics include nausea, vomiting, sedation, constipation, pruritus, and respiratory depression [19]. Due to a wide spectrum of opioid-induced adverse reactions, modern perioperative care promotes management methods and strategies aimed at reducing the opioid doses required yet providing appropriate efficacy of postoperative pain therapy and patient comfort. This aim can be achieved using multimodal analgesia, in which block anaesthesia techniques and pharmacotherapy with non-opioid analgesics and co-analgesics (lidocaine, ketamine, gabapentinoids) are essential [20].

In the postoperative period, opioids can be administered via a variety of routes; intravenous and oral routes are most commonly used, while in cases of nerve blocks the perispinal (epidural or subarachnoid) or perinervous route can be applied. It is worth emphasising that analgesics should not be administered intramuscularly for many reasons, including those which are obviously humanitarian. Furthermore, the subcutaneous route is not recommended due to body cooling commonly observed in the immediate postoperative period and unreliable drug absorption, thus difficult-to-anticipate analgesic effects. After extensive surgical procedures, opioids are most commonly administered intravenously due to excellent possibilities of adjusting their dose to the severity of pain. The optimal management strategy is to determine the most effective opioid dose by titration, i.e. the administration of low doses at short intervals until the pain is satisfactorily relieved, followed by continuous intravenous infusions. Titration is mainly recommended in patients with extremely severe pain in order to provide quick control, as well as in patients treated with potent opioids who additionally require many rescue doses of opioids. In practice, in cases of morphine titration, 1-2mg of i.v. morphine is administered at several-minute intervals (every 3-5 minutes) until significant satisfactory pain relief has been provided or adverse reactions have

Table 3. Doses of the opioid drugs most frequently used with patient-controlled analgesia in adult patients [19]

Opioid	Bolus dose	Refraction time (min)
Morphine	0.5–2.5 mg	5–15
Oxycodone	0.03 mg kg ⁻¹	5–10
Fentanyl	0.02–0.05 mg	5–10
Nalbuphine	1–3 mg	6–10
Tramadol	10–25 mg	5–10

occurred. Subsequently, based on the total analgesic dose and half-life of a drug (in this case - morphine), an hourly demand can be calculated. For instance, if the dose needed for effective analgesia is 12 mg of morphine, the patient should be administered a continuous intravenous infusion at a dose of 2 mg per hour – the half-life of morphine is 3-4 hours, which means that during that time half of a saturating dose (6 mg) has to be given to maintain the therapeutic concentration of morphine. Doses of the most common opioid drugs used with patient-controlled analgesia (PCA) in adults are presented in Table 3 [19].

In the immediate postoperative period, short-acting opioids are preferable due to better possibilities of modification of the analgesic dose; long-acting and controlled release preparations should be used during the following postoperative days when the pain being experienced is more stable.

To convert intravenous doses of morphine into oral doses, a ratio 1:3 is used, i.e. if the daily demand for i.v. morphine is 20 mg, the equivalent oral dose will be 60 mg. For oxycodone, this ratio is 1:2. Once the demand for morphine has been titrated, morphine can be replaced by any opioid analgesic characterised by the desirable therapeutic and pharmacokinetic profile and the optimal spectrum of adverse effects for a particular patient.

The substitution of one opioid drug for another, called the rotation of opioids, is often required due to the ineffectiveness of treatment, changes in the nature of pain, or the occurrence of adverse reactions. The pharmacotherapy of pain uses the term of equianalgesic doses, which are defined as the doses of various opioids inducing the same analgesic effect. Table 4 presents equianalgesic doses of the most common opioid analgesics. The most important opioid drugs used in everyday practice are listed in Table 5.

UNRECOMMENDED OPIOID DRUGS

PETHIDINE

The current standards of acute and postoperative pain management in Poland and worldwide (American Pain Society 2016) do not recommend pethidine. The recommendation is justified and concerns its efficacy, as well as safety. Pethidine is a synthetic analgesic showing weaker analgesic effects, as compared with morphine. Besides affecting

Table 4. Equianalgesic doses of opioid drugs

Opioid	Intravenous dose	Oral dose
Morphine	10 mg	30 mg
Tramadol	100 mg	150 mg
Oxycodone	7.5–10 mg	20 mg
Fentanyl	0.1 mg	–
Buprenorphine	0.4 mg	0.8 mg (sublingual tablets)
Tapentadol	–	100 mg
Methadone	1 mg	3 mg
Nalbuphine	10 mg	–

mu-opioid receptors, it exerts a cholinolytic effect and has locally anaesthetic action. After its parenteral administration, the analgesic effect is maintained for about 2–3 h and is individually variable. Norpethidine, an active metabolite of pethidine, is characterised by a long half-life of 8–21 h; although it has half the analgesic potency of pethidine, it exerts neurotoxic effects. Due to the short analgesic effect of pethidine and a long half-life of its neurotoxic metabolite, the latter can accumulate at repeated doses of pethidine. The prolonged half-life of norpethidine is particularly important in the paediatric population. Moreover, the use of pethidine during delivery may lead to the newborn's exposure as a result of placental drug transfer, which is likely to deteriorate the neonate's neurological status or even induce seizures. It should be emphasised that the blood-brain barrier in newborns and infants is not fully functionally efficient and therefore many drugs can more profoundly penetrate the CNS during this period, inducing post-drug adverse reactions, as compared with the population of adult patients. Therefore, pethidine should not be used as an analgesic during deliveries.

The adverse effects of pethidine may also be observed in the geriatric population. Patients over 65 years of age often have impaired liver and kidney functions compared with younger individuals, which additionally favours the accumulation of pethidine resulting from the prolongation of its half-life. Moreover, the administration of pethidine in this group increases the risk of CNS-associated adverse effects, including agitation, confusion, motor disturbances, dizziness, nausea and vomiting. Of note is the fact there are no data proving the higher efficacy of pethidine in the pharmacotherapy of pain compared with other opioids. Numerous studies have demonstrated that pethidine can be successfully replaced with other safer opioids that do not yield toxic metabolites, whose half-life and analgesic effects are substantially longer, as compared with pethidine.

PENTAZOCINE

Pentazocine is a kappa-opioid receptor agonist; therefore, besides relatively weak analgesic action (5–10 times weaker than that of morphine), it also shows hallucinogenic and dysphoric effects. For this reason, this drug should not be used for postoperative pain management [19].

NON-OPIOID ANALGESICS FOR POSTOPERATIVE PAIN MANAGEMENT

In patients with acute and postoperative pain, non-opioid analgesics are recommended when the severity of pain does not exceed NRS = 4. They can be administered as monotherapy; in cases of more severe pain, they should be part of multimodal analgesia, which allows one to broaden the spectrum of analgesic effects of other analgesics and to reduce the total dose of opioid analgesics.

In any nociceptive pain (mechanical, inflammatory, visceral), nonsteroidal anti-inflammatory drugs (NSAIDs) are effective. Paracetamol, which has no anti-inflammatory effects, is effective only in somatic nociceptive pain [19, 21, 22]. Metamizole is additionally characterised by central spasmolytic action; therefore, it is particularly effective in visceral nociceptive pain [22]. When NSAIDs are combined with paracetamol and/or metamizole, an additive analgesic effect is achieved.

The selection of NSAID for the treatment of postoperative pain should be individualised; the following criteria should be considered:

- onset of analgesic action,
- duration of analgesic effects
- effective analgesic dose
- contraindications and risk of upper gastrointestinal, cardiovascular and renal complications
- liver and kidney function,
- other drugs used simultaneously and potential interactions with non-opioid analgesics [21–23].

Intramuscular and rectal routes of administration of non-opioid analgesics are not recommended due to a long latency period and the fluctuating profile of analgesic effects (strong recommendation, I A) [22–24]. As intravenous drugs induce the quickest analgesic effects in acute pain, certain available i.v. drugs are recommended. Non-opioid analgesics achieve T_{max} (max. concentration) most quickly after i.v. administration, which directly correlates with the onset and peak of analgesic action [22–24]. Considering the pathomechanism of action, the location of pain, contraindications and limitations, the first-line drugs recommended for the treatment of acute and postoperative pain include dexketoprofen, ketoprofen, paracetamol and metamizole [22–24]. When analgesics can be administered orally, drugs in the form of granulates, soluble tablets and orodispersible

Table 5. The most common opioids used for postoperative pain relief

Opioid	Mechanism of action	Dosage	Comments
Tramadol	1. Mu-opioid receptor agonist 2. Inhibitor of noradrenalin and serotonin reuptake	Intravenously: in fractionated doses 50–100 mg every 4–6 hours or in a continuous i.v. infusion Orally: a short-acting preparation — 50–100 mg every 4–6 hours; a controlled-release preparation — 50–200 mg every 12 hours. The max. dose — 400 mg 24 h ⁻¹	The potency of tramadol is 1/10–1/6 of that of morphine. CYP2D6-mediated metabolism characterised by polymorphism and its genetically conditioned variants can induce weaker analgesic effects of tramadol in slow metabolisers (about 7–10% of Caucasians) or toxic effects even after a low dose of tramadol in rapid metabolisers (about 3% of Caucasians). Moreover, lower efficacy of tramadol is found in patients receiving simultaneously CYP2D6 inhibitors (e.g. paroxetine), ondansetron (serotonin receptor antagonist of ondansetron) and carbamazepine (CYP3A4 induction and intensification of conversion of tramadol into non-active N-desmethytramadol metabolite) A risk of potentially life-threatening serotonin syndrome in patients receiving tramadol combined with some drugs, such as <i>fluoxetine, sertraline, paroxetine, escitalopram, venlafaxine, duloxetine, clomipramine, amitriptyline, trazodone, risperidone</i> Tramadol should be avoided in patients with head injuries, disorders of consciousness, elevated intracranial pressure, or epilepsy. Poor potential of inducing drug dependence and tolerance. A lower risk of respiratory depression, as compared with other opioids
Morphine	Mu-opioid receptor agonist	In postoperative pain, intravenously, optimally using PCA (bolus 0.5–2.5 mg, refraction time 5–10 minutes) or titration: 1–2 mg every 3–5 minutes until the desired effect is achieved with continuation of continuous infusion. Orally, at a dose of 5–10 mg every 4 h (short-acting preparations) or 10–20 mg every 12 h (controlled release preparations) The conversion ratio of i.v. to oral morphine is 3: orally — a threefold higher dose of morphine compared with the dose that was effective during intravenous administration	Drug of linear pharmacokinetics — proportional dose–analgesic effect relationship; metabolised to morphine-3-(M-3G) and morphine-6-glucuronide (M-6G). M-3G can exert neurotoxic effects and induce seizures. It results in good mood, euphoria (dysphoria — although less frequently); reduces the ability to concentrate and slows down thinking processes; acts depressively on the respiratory centre — reduces the respiratory rate (even to apnoea); depresses the cough centre; constricts pupils; stimulates the chemoreceptor trigger zone, which leads to nausea and vomiting; causes the release of histamine; increases the tone of gastrointestinal muscular layer, especially of sphincters; impairs peristalsis; increases the urinary sphincter tone. In patients with neoplasms, an additional effect of alleviating dyspnoea is used
Oxycodone	Mu- and kappa-opioid receptor agonist	In postoperative pain, optimally — intravenous PCA (bolus 0.03 mg kg ⁻¹ , refraction time 5–10 minutes) or titration: 1–2 mg every 3–5 minutes until the optimal effect is achieved with continuation of continuous infusion Orally, controlled release preparations, initially 10–20 mg every 12 h. The conversion ratio of i.v. to oral oxycodone is 2, i.e. an oral dose twice as high as compared with the effective i.v. dose	Analgesic effects 1.5–2-fold stronger than those of morphine. The kappa-opioid receptor activity of oxycodone explains its higher efficacy in visceral pain relief, compared with other opioids. Therefore, oxycodone should be the opioid of choice in the treatment of postoperative pain after gastroenterological, urological and gynaecological procedures. Compared with other opioids, oxycodone less frequently induces gastrointestinal adverse reactions. It is a safe opioid analgesic for elderly patients not requiring dosage modifications, provided that liver and kidney functions are normal. Compared with morphine, oxycodone less commonly induces cognitive impairment in this age group of patients. It has a slight potential of drug interactions. Interactions with CNS depressive drugs and cholinolytic drugs can be clinically important. A preparation comprising oxycodone and haloxone (2:1) is available for oral administration, which is indicated for treatment and prevention of opioid-induced constipation
Fentanyl	Mu-opioid receptor agonist	Intravenously — continuous infusion at a dose of 0.5–3 µg kg ⁻¹ h ⁻¹ or using PCA: bolus 0.02–0.05 mg, refraction time 5–10 minutes. In chronic pain — transdermally, patches releasing 12.5, 25, 50, 75 and 100 µg fentanyl h ⁻¹ ; duration of action — 3 days	It is 50–80 times more potent than morphine yet shows a weaker sedative effect; only slightly releases histamine; metabolised to non-active metabolites in the liver, it can be used in patients with impaired renal function. A quick onset of action — after i.v. administration about 10 seconds and short action — on average 0.5–1 h after i.v. administration of 0.1 mg It is mainly used intraoperatively; in the postoperative period — used less frequently and mostly in continuous infusions, due to its short action. Thanks to its low molecular weight and high lipophilicity, fentanyl was the first opioid used transdermally for the treatment of chronic pain

Table 5 cont. The most common opioids used for postoperative pain relief

Buprenorphine	1. Mu-opioid receptor partial agonist 2. Delta- and kappa-opioid receptor antagonist	In postoperative pain — intravenously, 0.3–0.6 mg every 6–8 h. In chronic pain, transdermally with controlled release (releasing 35; 52.5 and 70 µg of buprenorphine per h)	Buprenorphine is 100 times more potent than morphine. In therapeutic doses, it acts as a pure agonist; the dose-analgesic effect relationship is linear. Ceiling effect for respiratory depression; therefore, the probability of its occurrence is low Its effects on cognitive functions in the elderly are slight. A low risk of tolerance compared with other opioids. In patients with kidney failure, the pharmacokinetics of buprenorphine changes and, thus, it can be safely used in this group of patients. Moreover, it has been demonstrated that buprenorphine is not eliminated during haemodialysis, which allows one to provide stable analgesia and prevents significant increases in pain after haemodialysis
Tapentadol	1. Mu-opioid receptor agonist 2. Noradrenalin reuptake inhibitor	Orally: immediate-release tablets at a dose of 50–100 mg every 4–6 h (max. daily dose — 600 mg) and controlled-release tablets at a dose of 50–250 mg every 12 h (at a maximum of 500 mg 24 h ⁻¹)	Its analgesic effect is 2–3-fold weaker than that of morphine. Unlike tramadol, it does not act on the serotonergic system. A low risk of drug interactions. Tapentadol should not be combined with MAO inhibitors (risk of hypertensive crisis) Low releasing potential; well tolerated also by elderly patients. The noradrenergic mechanism of action contributes to good efficacy of tapentadol in neuropathic pain and mixed pain with a neuropathic component
Nalbuphine	1. Mu-opioid receptor antagonist 2. Kappa-opioid receptor agonist	Intravenously — bolus 0.1–0.3 mg kg ⁻¹ (max. 20 mg), the dose can be repeated every 3–6 h, intravenous infusion — 0.04–0.32 mg kg ⁻¹ h ⁻¹	Nalbuphine should not be used together with pure mu-opioid receptor agonists as it abolishes their analgesic effects. Moreover, nalbuphine is not recommended in patients addicted to opioids or individuals treated chronically with opioids due to the risk of markedly increased pain and withdrawal syndrome. Slight addictive potential. The drug does not act on the smooth muscular layer of the GI and urinary tracts, thus minimally delays gastric emptying and intestinal passage and does not induce difficulties in urination. Compared with other potent opioids, its respiratory depression potential is lower; the ceiling effect is observed at a dose of 30 mg. The ceiling analgesic effect is observed at a dose of 50 mg Therefore, nalbuphine is also recommended for moderate pain
Methadone	1. Mu-opioid receptor agonist 2. N-methyl-D-aspartate (NMDA) receptor antagonist 3. Serotonin reuptake inhibitor	Orally — usually 2.5–10 mg every 3 to 8 h. Individual dosing and strict monitoring of analgesic action and adverse reactions are necessary	Methadone is used for chronic pain management. The tendency to accumulate in tissues is observed at repeated administrations Long and extremely changeable time of elimination, i.e. 15–60 h — once doses are changed, the steady state in serum is achieved not earlier than within several days. A risk of serotonin syndrome in patients treated with methadone combined with sertraline, venlafaxine and ciprofloxacin. Methadone can prolong the QT interval, which in patients treated with high doses of methadone combined with such drugs as haloperidol, TCA or ciprofloxacin can cause life-threatening arrhythmias

PCA: patient-controlled analgesia; MAO inhibitors: monoamine oxidase inhibitors; TCA: tricyclic antidepressants

Table 6. Maximum daily doses of nonsteroidal anti-inflammatory drugs most commonly used for acute pain

Drug	Maximum daily dose
Dexketoprofen	150 mg*
Ketoprofen	200 mg
Ibuprofen	3200 mg
Naproxen	1500 mg
Nimesulide	200 mg
Lornoxicam	16 mg
Diclofenac	150 mg

*p.o. max. 75 mg, i.v. max 150 mg

tablets (ODTs) are preferable due to the speed of analgesic action. The soluble formulations induce quicker analgesic effects than tablets, as once they are dissolved, the absorption is immediate and no time is needed to disintegrate the tablet and release an analgesic from it. Moreover, soluble formulations of NSAIDs available on the market may be taken on an empty stomach (e.g. dexketoprofen in the form of a soluble granulate for oral administration). The ceiling doses of all non-opioid analgesics have been determined, above which no increase in the analgesic effect is observed while the risk of complications is significantly higher [22–25] (Table 6).

The maximum daily doses of non-opioid analgesics are as follows:

- 5 g for metamizole,
- $\leq 15 \text{ mg kg}^{-1} \text{ mc}^{-1}$ for both oral and intravenous paracetamol; intravenously, the drug can be administered at a maximum of 4 times a day (in a patient weighing 80 kg, the daily dose of 4 g should not be exceeded) [26].

The use of paracetamol is associated with reduced severity of pain thus reduced consumption of opioid analgesics [26]. A single pre-emptive intravenous dose administered 10–30 minutes before skin incision reduces the severity of postoperative pain, decreases the incidence of nausea and vomiting and contributes to reduced use of opioid analgesics in the postoperative period, which diminishes the severity of adverse effects characteristic of this group of opioid analgesics. Of note is the fact that during the first post-surgery days, depending on the degree of pain severity de-escalation, the intravenous route is preferred; due to its pharmacokinetic/pharmacodynamic (PK/PD) profile, this route is associated with achieving higher concentrations of the drug, which translates into a more optimal profile of efficacy, as compared with the oral route, while it should be remembered that pharmacokinetics of paracetamol are linear [26].

Moreover, oral combinations of non-opioid analgesics are recommended for the treatment of acute pain. There

are such combinations available on the market which show an additive analgesic effect, e.g. paracetamol with ibuprofen. In practice, this means that such a combination supplements the pharmacological effects, broadening the spectrum of analgesic action while simultaneously only slightly potentiating this action. Furthermore, combinations showing hyperadditive effects are available, e.g. dexketoprofen + tramadol, paracetamol + tramadol, which means that the spectrum of analgesic effect is not only substantially supplemented and broadened but also the effect is markedly potentiated [22–24]. Acute and postoperative pain is also treated with such NSAIDs as selective COX-2 inhibitors. In Poland, oral forms of celecoxib and etoricoxib are available. According to the Cochrane Collaboration of 2013, celecoxib administered in a single dose after surgery (orthopaedic or dental procedures) effectively reduces the pain experienced and lengthens the time to administration of the next analgesic — median 6.6 h at 200 mg, 8.4 h at 400 mg and 2.3 h when a placebo is used. The adverse reactions have been observed in a comparable percentage of patients in the celecoxib and placebo groups and were mild or moderate [24, 25]. Schroer *et al.* [26], who studied the use of celecoxib for 6 weeks in 107 patients subjected to knee endoarthroplasty, demonstrated a lower consumption of opioids in the perioperative period and better VAS scores. Moreover, in the group receiving celecoxib over one post-surgery year, the range of motion at the knee joint was greater [24, 25]. Similar results were reported by other centres. The meta-analysis of studies regarding the prevention of extra-skeletal ossifications after hip endoarthroplasty has revealed that the efficacy of celecoxib in preventing extra-skeletal ossifications is comparable to that of indometacin. Furthermore, celecoxib was the only drug reducing the risk of gastrointestinal adverse effects (as compared with indometacin) [24, 25], which is extremely important in surgical patients who have to be subjected to obligatory assessment and receive pharmacological prophylaxis in justified cases of venous thromboembolic disease. It is worth pointing out that the use of celecoxib does not exclude upper gastrointestinal complications, including perforation. However, when applied according to experts' recommendations, it significantly reduces their risk, compared with non-selective cyclooxygenase inhibitors. Another drug that has been found to provide adequate acute and postoperative pain management is etoricoxib [24, 25].

PARACETAMOL

Based on the most recent studies concerning its mechanism of action, paracetamol is considered a pro-drug, which interacts with the endocannabinoid system thanks to its active metabolites. In the brain and spinal cord, paracetamol has been found to undergo deacetylation to p-aminophe-

nol, which reacts with arachidonic acid via fatty acid amide hydrolase (FAAH) to form an active metabolite of this drug, i.e. N-arachidonoylphenolamine (AM404) [27, 28], that does not directly affect the cannabinoid receptors but indirectly increases the activity of the endocannabinoid system. On the one hand, this compound is a potent activator of the transient receptor potential cation channel subfamily V member 1 (TRPV1), which is a ligand of cannabinoid type 1 (CB1) receptors; on the other hand, being an inhibitor of endogenous cannabinoid (anandamide) reuptake, it increases the endogenous pool of these compounds [29]. Endogenous cannabinoids, e.g. anandamide, exert antinociceptive effects both at the level of the spinal cord and the brain. Moreover, cannabinoids substantially reduce body temperature by activating CB1 receptors in the pre-visual hypothalamic area [27, 29, 30]. It is well known that analgesic derivatives of aniline show similar effects as those of cannabinoids, e.g. improved mood, mental relaxation and tranquillity. To date, such properties of paracetamol have not been demonstrated, although some authors attribute slight sedative effects to it. Moreover, AM404 has been found to show dose-dependent COX-1 and COX-2 inhibitory effects [27, 28, 30, 31]. This mechanism may be particularly important in the brain areas with high concentrations of FAAH, e.g. in the mesencephalic nucleus of the trigeminal nerve or in the primary sensory neurones, as the production of AM404 in these areas is increased, which can to some extent explain the inhibitory activity of paracetamol toward CNS cyclooxygenases. An alternative mechanism of the analgesic effects of paracetamol could be the inhibition of nitric oxide (NO) formation. The L-arginine/NO pathway, activated by substance P and N-methyl-D aspartic acid (NMDA) receptors, leads to the synthesis of NO, which is an important neurotransmitter in the nociceptive processes in the spinal cord [30–32].

In conclusion, paracetamol acts at all levels of conduction of pain stimuli, starting with the receptors in tissues, through the spinal cord to the thalamus and cerebral cortex, where the pain sensations are received. The mechanism of analgesic action of paracetamol is complex and still several options are considered, including the effects on both peripheral (inhibition of COX activity) and central (COX, descending serotonergic inhibitory pathways, L-arginine/NO pathway, the cannabinoid system) anti-nociceptive processes and the “oxidoreductive” mechanism. Currently, the inhibitory effects of paracetamol on COX-3 are no longer emphasised as COX-3, which occurs in laboratory animals, has not been detected in humans [32].

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-drugs (NSAIDs) belong to the group of non-opioid analgesics of anti-inflammatory, analgesic and

antipyretic action. In addition to inhibiting the synthesis of prostaglandins, they may affect other pathophysiological processes involved in inflammatory nociceptive pain. This group of drugs exerts analgesic and anti-inflammatory effects via inhibition of inducible nitric oxide synthase expression and of NF-kappa B activation, activation of the system of lipoxines, as well as inhibition of substance P activity. Additionally, the action of NSAIDs may result from activation of supraspinal cholinergic pathways and of the system of endogenous opiate-similar peptides.

In patients treated with NSAIDs, contraindications and limitations resulting from cardiovascular, kidney, upper and lower gastrointestinal diseases should be taken into account. As far as perioperative interactions are concerned, it is worth remembering that their concomitant use with the drugs belonging to selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) increases the risk of perioperative bleeding. Likewise, their concomitant administration with loop diuretics increases the risk of nephrotoxicity. Only one NSAID should be applied at a time, as more NSAIDs do not increase the therapeutic efficacy while significantly increasing the risk of adverse effects. Acute and postoperative pain is also treated with such NSAIDs as selective COX-2 inhibitors. In Poland, oral celecoxib and etoricoxib are currently available.

METAMIZOLE

Among the drugs having analgesic, antipyretic and relaxing effects, metamizole is most commonly used in Poland [33–35]. Metamizole belongs to the group of non-opioid analgesics. Unlike NSAIDs, it shows no anti-inflammatory action; however, its analgesic effect cannot be compared with that of any other analgesic [35–38]. In 2012, new metamizole metabolites were identified, which changed the general approach to the use of metamizole in ambulatory and clinical practice. This regards not only wider clinical indications but also new options for combined treatment [35, 39, 40]. The metabolites of metamizole inhibit the synthesis of prostaglandins, mainly by inhibiting COX-1 and COX-2 activity but also by inhibiting substance P-induced nociception [35, 36, 39–42]. Additionally, metamizole affects the cannabinoid system, producing analgesic and antipyretic effects [35, 43, 44]. Furthermore, the relaxing smooth muscle effect results from the inhibition of adenosine reuptake in the CNS structures and the influence on the cannabinoid system. The relaxing effect is particularly important for the management of colic and visceral pain [36, 44, 45]. Metamizole displays a synergism of action with NSAIDs, paracetamol and opioid analgesics. It is recommended for acute pain, including post-trauma pain and as a relevant element of the combined treatment of pain. Considering new data demonstrating its safety, metamizole may be used both in

adult and paediatric populations. In 2014, metamizole was included in the Austrian standards regarding its use in the paediatric population, which has consolidated the opinion about its safety in this population. Furthermore, in Poland there are some approved therapeutic products containing metamizole that may be used in infants over 3 months of age. According to recent cohort and observational studies, metamizole-induced agranulocytosis is rare while its incidence is comparable to that induced by other non-steroidal analgesics [36, 39, 46]. The use of metamizole is associated with a low risk of interactions with other drugs applied concomitantly. As the interaction with cyclosporine is clinically important, great caution should be exercised in patients receiving both drugs simultaneously.

ADJUVANTS FOR ACUTE PAIN MANAGEMENT

Note:

1. The information provided below does not include the use of the drugs discussed in regional anaesthesia.
2. The use of the drugs discussed below as adjuvants for pain relief/components of multimodal analgesia is outside the summary of therapeutic product characteristics (except lidocaine).

LIDOCAINE

Intravenous lidocaine used in the perioperative period as part of multimodal analgesia allows one to administer lower doses of opioids or to abandon them completely. It significantly decreases the severity of pain in the early postoperative period at rest and during physical activity (deep breaths, coughing). Moreover, its use significantly reduces the incidence of nausea and vomiting, accelerates the restoration of postoperative gastrointestinal function (particularly after abdominal surgeries) and shortens hospitalisation stays ([47–51] meta-analyses of randomised controlled trials [RCT] = level I). Furthermore, perioperative intravenous infusions of lidocaine have been demonstrated to induce preventive analgesia (analgesia of 5.5-times longer action than the half-life of lidocaine, i.e. > 8 h since the discontinuation of its administration ([52] meta-analysis of RCT = level I).

According to the results of clinical trials, intravenous infusions of lidocaine are predominantly indicated in open and laparoscopic abdominal surgical procedures. Few clinical trials demonstrate the benefits of intravenous infusions of lidocaine in patients subjected to prostate, breast, thoracic and multi-level spinal procedures. No benefits have been confirmed in patients after cardiac surgeries, laparoscopic nephrectomy, transabdominal hysterectomy or hip endoarthroplasty [53].

Optimal dosage, initiation and duration of lidocaine intravenous infusion have not yet been determined. The

available clinical trials show that the intravenous infusion of lidocaine is initiated at least 30 minutes before skin incision (induction of preventive analgesia), up to 30 minutes before or during the induction of anaesthesia. The most common saturating bolus dose is 1.5 mg kg^{-1} (dose range $1\text{--}3 \text{ mg kg}^{-1}$), while the lidocaine dose in an infusion ranges from 1.5 to $3.0 \text{ mg kg}^{-1} \text{ h}^{-1}$. Doses should be calculated based on the ideal body weight (IBW), which is particularly important in obese patients. The infusion ends at the completion of surgery (in most cases) or is continued in the postoperative period — most commonly over 24 hours or up to 48 h [54]. With the above doses, the plasma concentration of lidocaine can fluctuate between 1 and $5 \mu\text{g mL}^{-1}$. Lidocaine administered in such doses does not block peripheral nerve conduction. From the pharmacological point of view, intravenous lidocaine is a modulator of conduction in the peripheral nervous system and of peripheral and central sensitisation [55].

The dose of lidocaine should be reduced in cases in which the free drug fraction is increased, namely: acidosis, hypercapnia, hypoxia, hypoproteinaemia, and impaired liver and kidney functions. In patients with heart, liver and/or kidney failure, the dose of lidocaine should be reduced and the cardiovascular system should be monitored [56].

The infusion of lidocaine is contraindicated when other modalities of regional anaesthesia are applied, especially when a local anaesthetic is administered in a bolus or high doses (e.g. epidural anaesthesia, plexus anaesthesia). An infusion may be initiated 4–8 h after bolus administration of the local anaesthetic, if required. In cases of failed epidural anaesthesia, once the continuous infusion into the epidural space is stopped and no bolus doses are given into the epidural space, the continuous intravenous infusion of lidocaine can be initiated immediately, albeit without an intravenous bolus [57].

Lidocaine in a continuous infusion at a dose of $\geq 2 \text{ mg kg}^{-1} \text{ h}^{-1}$ reduces pain severity at rest within the first 4 postoperative hours [58]. According to one study in which $1.5 \text{ mg kg}^{-1} \text{ h}^{-1}$ lidocaine in a continuous infusion was used, there were no differences in pain severity compared with the control group; however, the demand for morphine was found to be lower while pain on movement was found to be of lesser severity. The differences occurred on the second postoperative day and were most pronounced during the third postoperative day [58]. The above observations are consistent with the results of laboratory tests, which reveal that the infusion of lidocaine inhibits the development of central hyperalgesia in three phases. The first acute phase of inhibition lasts 30–60 minutes after the completion of the infusion; the second transient phase, up to 6 hours; while the third phase of prolonged inhibition develops slowly within 24 h after the completion of the infusion and is maintained for 21 days [59].

In acute neuropathic pain (which can be a component of postoperative pain), the action of lidocaine involves mainly the inhibition of generation of ectopic, spontaneous excitations in the damaged nerves. Such effects occur at a plasma concentration of lidocaine 40 times lower than the concentration that is required to inhibit the conduction of nerve excitations in undamaged nerves [60].

The mechanism of action of lidocaine in postoperative pain differs from the mechanisms of its action in neuropathic pain and is not fully elucidated. It does not affect acute nociceptive pain [61–64]. Moreover, lidocaine does not significantly influence the thermal and mechanical pain threshold in intact tissues [64, 65]. It acts anti-hyperalgesically inhibiting peripheral sensitisation by affecting C-fibre nociceptors (primary hyperalgesia), as well as central sensitisation at the spinal cord level (secondary hyperalgesia). The central effects predominate. The perioperative infusion of lidocaine is most effective in surgeries associated with the development of increased central hyperalgesia.

Two large groups of C-fibre nociceptors are distinguished, namely: those mechanically and heat-responsive (CMH); and those unresponsive to mechanical and heat stimulation (CMiHi), called “sleeping” nociceptors, which become stimulus-responsive after their sensitisation (a decrease in the excitation threshold) by mediators of inflammation (reduction in nociceptors). The sensitisation of polymodal nociceptors leads to temporal summation of nociceptive stimuli while the recruitment of “sleeping” nociceptors leads additionally to spatial summation [66, 67].

Lidocaine preferentially affects the recruited nociceptors and inhibits their activity (by blocking sodium channels Nav 1.7, 1.8 and 1.9), thus decreasing primary hyperalgesia. It does not affect CMH nociceptors; the threshold to mechanical and thermal stimuli (including acute nociceptive pain) remains unchanged and can mask the analgesic effect of lidocaine [68–70]. Stronger inhibition of sensitised “sleeping” CMiHi receptors by low concentrations of lidocaine seems to be the cause of the high efficacy of intravenous infusions of lidocaine in gastrointestinal surgical procedures. In abdominal surgeries with extensive tissue damage, potent stimulation of nociceptors responsive to chemical stimuli and the simultaneous sensitisation of CMiHi nociceptors are observed. By inhibiting these nociceptors, lidocaine reduces central hyperalgesia and postoperative pain [71].

Lidocaine acting at the spinal cord level inhibits synaptic conduction, thus reducing secondary hyperalgesia [72–74]. The synaptic conduction effects result from direct and indirect (inhibition of protein kinase C) blocking of NMDA receptors and neurokinin receptors. The inhibition of M3 muscarinic and glycine receptors enhances the activity of the descending cholinergic antinociceptive system [75–77].

A relevant mechanism of lidocaine action in acute pain is its anti-inflammatory action (a more detailed description is beyond the scope of this paper) [78]. This drug limits the inflammatory reaction to surgery-related trauma by blunting the effects of proinflammatory factors. It inhibits granulocyte priming, which prevents the excessive release of proinflammatory cytokines and free radicals. The activity of mechanisms leading to the development of neurogenic inflammation is diminished at the site of tissue damage, which decreases peripheral sensitisation and primary hyperalgesia [79].

MAGNESIUM SULPHATE

Magnesium is an antagonist of NMDA receptors present in the peripheral and central nervous system [80]. The NMDA receptors are an important element of the glutamatergic system whose main neurotransmitter is glutamic acid (glutamate). One of the functions of the glutamatergic system is the involvement in nociception. The excitation of NMDA receptors by glutamate causes an intracellular inflow of calcium ions and enhances the propagation of nociceptive impulsation. The concentration of NMDA receptors is particularly high in the anterior horns of the spinal cord. These receptors are associated with the development of central sensitisation clinically manifesting itself as hyperalgesia and allodynia [81, 82]. Besides inhibiting NMDA receptors, magnesium ions exert anti-inflammatory effects by decreasing the plasma concentration of IL-6 and TNF- α . The anti-inflammatory action can be involved in the reduction in central sensitisation [83].

Magnesium sulphate added to i.v. morphine reduces the daily demand for morphine (opioid-sparing effect) in the postoperative period. Although this does not affect the incidence of nausea and vomiting, it decreases the severity of pain at rest, especially during the first 4–6 hours, at a maximum of up to 20–24 hours after surgery, and on movement up to 20–25 hours after surgery ([84] RCT meta-analysis = level I, [85] RCT meta-analysis = level I, [86] RCT meta-analysis = level I, [87] RCT meta-analysis = level I [88], RCT meta-analysis = level I). The most pronounced reduction in daily demand for morphine was observed after urologic, gynaecological and orthopaedic procedures, as well as cholecystectomies, large bowel procedures and coronary artery bypass grafting.

The uniform doses of magnesium sulphate have not been determined to date. In most cases, an initial bolus of 50 mg kg⁻¹ (range 30–50 mg kg⁻¹) is used, followed by intravenous infusion of 10–15 mg kg⁻¹ h⁻¹ (range 6–25 mg kg⁻¹ h⁻¹) until the surgery has been completed, although in some studies the infusion was continued for 24–48 hours. The beneficial effects of magnesium sulphate in the postoperative period were also observed in patients undergoing

subarachnoid anaesthesia ([89] RCT meta-analysis = level II, [90] RCT meta-analysis = level II, [91] RCT meta-analysis = level II]).

Magnesium ions can delay the restoration of neuromuscular transmission and induce bradycardia; nevertheless, the available data demonstrate that magnesium sulphate is an effective and safe complement of postoperative pain pharmacotherapy and should be considered as part of multidirectional (multimodal) analgesia.

ALPHA-2-ADRENOMIMETIC DRUGS (α 2-ADRENERGIC RECEPTOR AGONISTS)

Agonists of the α 2-adrenergic receptor exert their effects by stimulating α 2-receptors in the posterior horn of the spinal cord and supraspinally at the locus coeruleus.

The perioperative use of an α 2-adrenergic receptor agonist, clonidine or dexmedetomidine, diminishes the intensity of pain in the postoperative period, enables reductions in opioid doses and decreases the incidence of nausea ([92] RCT meta-analysis = level I). The above drugs are most commonly used in premedication (orally or intravenously) and intraoperatively (intravenously); their supply can be continued in the postoperative period (repeated doses or continuous infusions). The optimal dosage has not yet been determined.

Clonidine is most commonly administered as premedication at a dose of 3–5 $\mu\text{g kg}^{-1}$ (30–90 minutes before induction, orally or in a 30–60-minute intravenous infusion). Its supply can be continued in the intravenous infusion at a dose of 0.2–0.3 $\text{mg kg}^{-1} \text{h}^{-1}$ [93–95].

Dexmedetomidine is used at an initial dose in intravenous premedication (5–10 minutes to 30 minutes before induction) or intraoperatively in intravenous infusion at a dose of 0.5–2 $\mu\text{g kg}^{-1}$ administered over 5–10 minutes. The intravenous supply of dexmedetomidine is continued intraoperatively and/or postoperatively at a dose of 0.2–0.5 $\text{mg kg}^{-1} \text{h}^{-1}$ [96–99].

The most common adverse effects limiting the use of α 2-adrenergic receptor agonists include hypotension, bradycardia and sedation.

GABAPENTINOIDS (α 2A LIGANDS)

Gabapentinoids inhibit hyperalgesia and allodynia and only slightly affect nociception. They reduce hyperexcitation of neurones in the posterior horns of the spinal cord (leading to central sensitisation) developing after traumatic tissue damage.

Two phases of gabapentinoid action are distinguished, namely rapid (30–60 min) and slow (10–20 h). According to the studies performed to date, the rapid phase seems essential for acute pain in the perioperative period, which is associated with the effects on surgically damaged neurones.

In these neurones in the apparatus releasing a neurotransmitter, the number of calcium channels increases and the cell excitation is up-regulated.

Gabapentinoids bind to a subunit of the α 2 δ presynaptic high-voltage-gated calcium channel (HVA- Ca^{2+}), causing its inactivation. This limits the axonal transport of active HVA- Ca^{2+} channels to the synapse in the spinal cord and reduces their number in the neurotransmitter-releasing apparatus, which results in a decreased intracellular inflow of calcium ions necessary to initiate the release of a stimulating neurotransmitter (e.g. substance P, a peptide connected with the calcitonin gene) from the presynaptic vesicles. The reduced neurotransmitter release decreases the excitation of neurones, which results in quick emergence of the effects inhibiting the development of allodynia and hyperalgesia [100].

The perioperative use of gabapentin ([101] RCT meta-analysis = level I, [102] RCT meta-analysis = level II) and pregabalin ([103] RCT meta-analysis = level II) improves the quality of analgesia at rest and on movement while reducing opioid requirements in the postoperative period. Gabapentin and pregabalin reduce the incidence of adverse effects induced by opioids, especially vomiting, urine retention and nausea. According to the authors of a meta-analysis regarding perioperative pregabalin, the drug can be particularly beneficial for patients undergoing surgical procedures associated with highly severe postoperative pain and indications for its use should be determined after the potential side effects have been considered [104].

The beneficial effects of gabapentin on the severity of postoperative pain and opioid consumption were observed irrespective of the type of surgery [102] and dose (within the range of 300–1200 mg) [101], although the authors of a meta-analysis performed later suggest doses in the range of 600–1200 mg [102]. Given the diversity of dosing protocols, it is difficult to recommend one of them. Based on one's present knowledge, it seems justified to administer gabapentin in premedication 2 hours before surgery at a dose of 600–1200 mg, taking into consideration possible adverse reactions (excessive sedation, dizziness, vision disorders).

CORTICOSTEROIDS

Generally, acute postoperative pain is considered to be inflammatory nociceptive pain. Depending on the type of surgery, a neuropathic component to acute postoperative pain may develop. During the late acute phase of postoperative pain, reversible neuropathic pain is even likely to predominate [105].

Tissue damage triggers the arachidonic acid cascade, ultimately leading to the formation of algesiogenic prostaglandins and leukotrienes. The key process for the initiation of the arachidonic acid cascade is the activation of

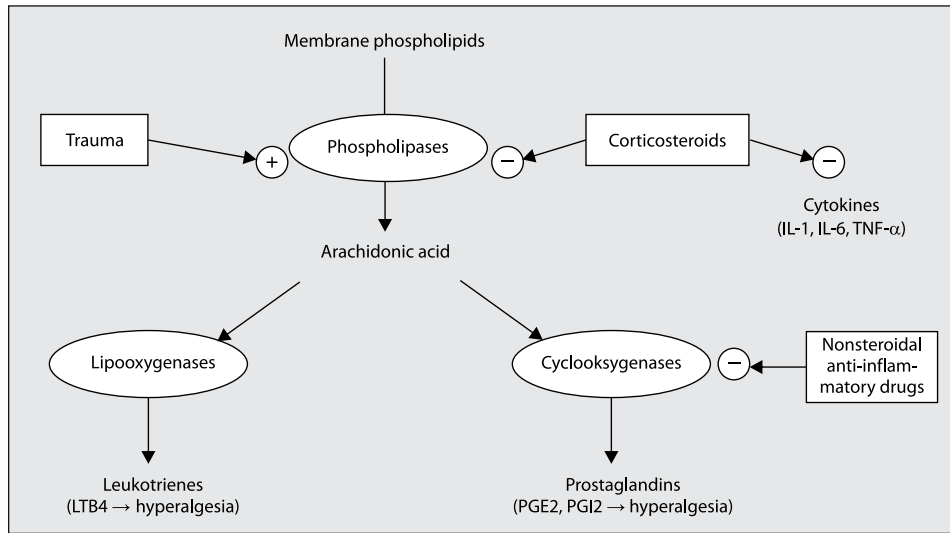


Figure 1. Scheme of the process of inhibiting phospholipase A2 activity by corticosteroids

phospholipase A₂ (PLA₂), which releases arachidonic acid directly from membrane phospholipids. Arachidonic acid is a substrate for cyclooxygenase (COX) and lipoxygenase (LOX). COX catalyses the synthesis of prostaglandins while LOX catalyses the synthesis of leukotrienes. PGE₂ and PGI₂, as well as leukotrienes LBT_{4r}, are involved in the development of hyperalgesia.

Corticosteroids indirectly inhibit the activation of phospholipase A₂ by inducing the synthesis of lipocortine (annexin A1). The inhibition of phospholipase A₂ reduces the amount of substrate (arachidonic acid) available for cyclooxygenase and lipoxygenase, which in turn results in reduced synthesis of prostaglandins and leukotrienes and finally produces anti-inflammatory effects [106].

Corticosteroids inhibit the formation and release of pro-inflammatory cytokines IL-1, IL-2, IL-6, interferon gamma (IFN-γ) and tumour necrosis factor alpha (TNF-α). They stabilise the cell membranes of neurones in the peripheral tissues and exert an antinociceptive effect at the spinal level.

The main mechanism of action of corticosteroids involves binding to an intracellular receptor (glucocorticoid receptor — GR). Via the genomic mechanism, after binding the corticosteroid, the GR-ligand complex formed is transported (translocation) to the cell nucleus. In the nucleus, the complex acts directly and indirectly on DNA transcription and thus affects the expression of target genes and the synthesis of proteins via transactivation or transrepression. The indirect inhibition of inflammatory response genes occurs by interacting with the transcription factors — activator protein 1 (AP-1), nuclear factor kappa B (NF-κB) and interferon regulatory factor 3 (IRF-3) [107]. The onset of action via the genomic mechanism is slow (several hours) [108].

Via the non-genomic mechanism, the corticosteroid-induced processes occur too quickly (minutes) to depend on the effects on DNA transcription. One such process is the inhibition of arachidonic acid release from membrane phospholipids (described above). During this short time corticosteroids are likely to modulate (stabilise) the excitability of the cell membrane and synaptic transmission by interacting with ionotropic receptors, such as GABA_A or NMDA, or with voltage-gated calcium or potassium channels [108].

The first clinical trials evaluating the effects of steroids on postoperative pain were carried out in patients after molar extractions in the 1980s [109, 110]. Since that time, many clinical trials have been published confirming the efficacy of steroids for reducing the severity of pain and opioid consumption in the postoperative period. Dexamethasone was used most frequently and methylprednisolone, betamethasone and hydrocortisone less frequently.

Patients receiving dexamethasone reported lower intensities of pain at rest and on movement and decreased opioid requirements in the postoperative period; the time to the first analgesic dose was found to be longer, a rescue analgesic dose was less frequently required and recovery room stays were shorter. The differences between the study and control groups were statistically significant, albeit clinically slight. The pain intensity was reduced by about 10%, as compared with the control group. Opioid requirements during the first 24 postoperative hours decreased by 10–13% ([111] RCT meta-analysis = level I, [112] RCT meta-analysis = level I, [113] RCT meta-analysis = level I).

Dexamethasone at a dose of 0.11–0.2 mg kg⁻¹ reduces the pain intensity and opioid demand in the postoperative period. A lower dose does not exert such effects whereas

a higher dose is not more effective ([114] RCT meta-analysis = level I). The analgesic action of dexamethasone is stronger when administered 45–90 minutes before surgery ([113] RCT meta-analysis = level I, [114] RCT meta-analysis = level I). A certain limitation to preoperative *i.v.* administration of dexamethasone might be a high incidence (50–70%) of strong, burning pain of the perineum, especially after the quick administration of a low volume. This can be prevented by diluting the drug in 50 mL 0.9% NaCl and giving it by an intravenous infusion for 10–15 minutes [113, 114].

A single dose of dexamethasone has not been found to increase the incidence of infections or to delay postoperative wound healing; however, during the first 24 postoperative hours, the blood concentration of glucose is slightly yet statistically significantly higher ([111] RCT meta-analysis = level I, [114] RCT meta-analysis = level I, [113] RCT meta-analysis = level I).

The use of dexamethasone for postoperative pain relief is best documented in patients undergoing the following: maxillofacial procedures ([115] RCT meta-analysis = level I); tonsillectomies (including those in children) [111] RCT meta-analysis = level I, [116] RCT meta-analysis = level I; thyroid surgeries [117] RCT meta-analysis = level I; and knee and hip procedures [118] RCT meta-analysis = level I, [119] RCT meta-analysis = level I.

A dose of 0.1–0.2 mg kg⁻¹ is most frequently used. For optimal analgesic effects, this should be administered about 45–90 minutes before surgery. The analgesic effects are maintained for up to 24 hours.

KETAMINE

The basic management to maintain homeostasis in a surgical patient involves the provision of adequate analgesia and sedation, as well as the blockage of afferent transmission of stimuli (including those which are nociceptive) to the CNS, haemodynamic stability, appropriate tissue perfusion and abolition of reflexes. In the postoperative period (including post-trauma), the therapeutic interventions should be focused on providing effective analgesia and haemodynamic stability. In order to achieve this, perioperative (post-trauma) opioid analgesics are used. According to some recent studies, however, patients are likely to develop opioid-induced immunosuppression, which may result in increased incidences of perioperative infections, an increased risk of complications (in elderly patients, in particular) [120, 121] and the risk of opioid-induced hyperalgesia (opioid paradox) resulting in higher intensity of pain, despite the escalation of doses of opioid analgesics [122, 123]. Moreover, opioid-induced adverse effects in the perioperative or post-trauma period, such as nausea, vomiting, impaired peristalsis, can significantly prolong the hospitalisation and favour perioperative complications. Therefore, the on-going studies are

focused on the optimisation of perioperative management, in which the use of opioid analgesics will be substantially limited or completely eliminated (opioid free anaesthesia/analgesia — OFA), which should enable the elimination of opioid-associated adverse reactions [124–126].

The above method involves multimodal management based on multifaceted pharmacotherapy and block anaesthesia techniques and is associated with:

- 1) the induction of a sympathetic nerve block:
 - direct: clonidine, dexmedetomidine, β -adrenolytics;
 - indirect: lidocaine, volatile anaesthetics, calcium antagonists;
- 2) the use of multimodal pharmacotherapy modulating nociception:
 - ketamine, dexmedetomidine, lidocaine *i.v.*, MgSO₄,
 - paracetamol, dexketoprofen, metamizole;
- 3) peripheral nerve blocks:
 - single/continuous infiltration anaesthesia,
 - interfascial blocks,
 - paravertebral blocks,
 - nerve and plexus blocks;
- 4) central blocks.

Considering the above, the use of ketamine, whose mechanism of action is multifaceted, enables one to provide effective OFA or to substantially reduce opioid doses. By inhibiting the activation of the NMDA receptor, ketamine induces analgesia and prevents the development of chronic postoperative pain [127, 128] whereas by activating adrenergic neurones and inhibiting synaptic reuptake of monoamines it determines haemodynamic stability in the perioperative and post-trauma period [129, 130]. Ketamine is also characterised by the lack of inhibitory effects on the respiratory centre; it dilates bronchioles, does not inhibit the upper respiratory reflexes [131] and blocks the activation of proinflammatory cytokines [132]. Moreover, its use is associated with a significantly lower incidence and severity of postoperative nausea and vomiting (level IA, according to evidence-base medicine (EBM) [133, 134]. Furthermore, the antidepressant action of ketamine used in sub-anaesthetic doses, associated both with the induction of brain-derived neurotrophic factor (BDNF) expression (BDNF concentration is reduced in patients with depression) and with glutaminergic neurotransmission block, is particularly useful in ICU patients after multiple organ injuries or extensive surgical procedures, as it can prevent post-traumatic stress syndrome [135, 136].

In clinical practice, sub-anaesthetic doses of perioperative ketamine are recommended, which provide haemodynamic stability and effective analgesia, and allow avoiding psychotomimetic symptoms. The suggested perioperative doses are presented in Table 7 [137].

Table 7. Perioperative sub-anaesthetic doses of ketamine [137]

Surgical procedures < 60 min; 0.1–0.3 mg kg⁻¹ *i.v.* bolus during induction

Surgical procedures > 60 min, with no *i.v.* infusion planned in the postoperative period; 0.1–0.3 mg kg⁻¹ *i.v.* bolus during induction, followed by boluses at a dose of 0.1–0.3 mg kg⁻¹ every 30–60 min

Surgical procedures > 60 min, with *i.v.* infusion planned in the postoperative period; 0.1–0.3 mg kg⁻¹ *i.v.* bolus during induction followed by *i.v.* infusion at a dose of 0.1–0.2 mg kg⁻¹ h⁻¹ over 24–72 hours. After 24 hours, a dose reduction to 10 mg h⁻¹ or less should be considered

It should be emphasised that due to the effects described above, ketamine is used in emergency medicine and battlefield medicine, where it effectively relieves acute pain accompanying the injuries to the thorax, abdomen, soft tissues and the skeletomuscular system [138–140].

The dosing protocol of ketamine in this group of patients is as follows:

- initial dose: 0.1–0.5 mg kg⁻¹
- followed by continuous *i.v.* infusion of 0.05–0.4 mg kg⁻¹ h⁻¹ [140, 141].

Moreover, in trauma patients, pre-hospital analgesic management involves intranasal applications of S-ketamine at a dose of 0.45–1.25 mg kg⁻¹ [142] or racemic ketamine at an initial dose of 0.7 mg kg⁻¹; when ineffective within 15 minutes, another dose is given — at 0.5 mg kg⁻¹ [143].

Acute pain accompanying diagnostic and therapeutic procedures in emergency departments and intensive care units is relieved with a mixture of ketamine and propofol, so-called ketofol, usually in the following doses:

- 1:4 (40 mg ketamine + 160 mg of propofol),
- 1:1 (0.5 mg kg⁻¹ ketamine + 0.5 mg kg⁻¹ propofol) [144–146].

CANNABINOIDS IN PAIN MANAGEMENT

Cannabinoids are organic chemical compounds, active substances interacting with the metabotropic cannabinoid receptors CB1 and CB2, produced endogenously in humans and animals – endocannabinoids (anandamide and arachidonyl glycerol), phytocannabinoids found in *Cannabis sativa* and *Cannabis indica* and synthetic cannabinoids. Cannabinoids naturally occurring in cannabis herbs have been used for medical purposes for centuries. Marijuana is also the most popular narcotic agent used for recreational purposes. In the 1940s, the use of cannabinoids was prohibited in the United States and many other countries. The active component is psychoactive Δ -9-tetrahydrocannabinol (THC), also responsible for many known effects; more than 60 chemical compounds were identified, including cannabidiol (CBD) and cannabitol (CNB) showing no psychoactive action.

The CB1 receptors located in the CNS and agonists of these receptors have euphoric, anti-seizure, analgesic, antiemetic and appetite-enhancing effects. As they are not present in the medulla oblongata, cannabinoids do not cause respiratory depression. The CB2 receptors are located

peripherally, have immunosuppressive and anti-inflammatory effects, modulating the release of proinflammatory cytokines (among other things). They are present in the respiratory and cardiovascular system, muscles and gastrointestinal tract. Under normal conditions, cannabinoid neurotransmitters (endocannabinoids) bound to cannabinoid receptors regulate homeostasis and the maintenance of cognitive functions, memory, appetite, heart rhythm, intraocular pressure and gastrointestinal peristalsis.

A systematic review of the available randomised controlled studies demonstrates that cannabinoids do not play any role in relieving acute, postoperative pain. Moreover, they have not been found to be effective for prevention of postoperative nausea and vomiting [147–149].

Cannabinoids may be used in cancer patients with the disease-associated symptoms or negative treatment outcomes, such as persistent nausea, vomiting, loss of appetite and pain, mainly neuropathic pain resistant to other forms of treatment. The above symptoms are predominantly related to chemotherapy and radiation therapy. Pre-clinical studies suggest that cannabinoids might be also effective for prevention of peripheral neuropathy after chemotherapy [150–152]. Cannabinoids used for a short time have an acceptable safety profile and the adverse effects are generally well tolerated and short-term. In conclusion, prescription cannabinoids should be available for patients with debilitating symptoms when other standard methods of treatment have failed [153, 154].

GENERAL RECOMMENDATIONS

PREOPERATIVE EDUCATION AND PLANNING OF PERIOPERATIVE PAIN MANAGEMENT

It is recommended to provide patients with information and knowledge of postoperative pain treatment options. The plan and goals of postoperative pain management should be documented (I C strong recommendation, low-quality evidence).

An individualised approach to preoperative education involves the provision of information that is age-appropriate, tailored to the patient and family level of comprehension, one's general knowledge about health, cultural and linguistic differences, and supported by opportunities to ask questions and receive authoritative and useful answers [155].

The administration of analgesics should be adjusted to the patient and their needs. An individual approach to perioperative analgesia should include preoperative evaluation of the patient, a physical examination and an assessment of their history regarding concomitant diseases, including mental health, concomitant drugs, the presence of chronic pain, earlier strategies of postoperative pain relief (I C, strong recommendation low-quality evidence) [156]. Moreover, it is important to evaluate opioid dependence or tolerance, as well as earlier and present consumption, as it may be associated with increased requirements for opioids in the postoperative period and inadequate analgesia [157].

Education or counselling should also include information about the way of reporting pain and its assessment (including tools for evaluating pain). Moreover, the goal of education should be to correct all false beliefs concerning pain and analgesics.

In the analgesic management plan, the efficacy of pain relief should be so adjusted as to minimise any adverse effects (IC strong recommendation, low-quality evidence).

Optimal pain treatment should be provided with suitably frequent assessment of pain relief adequacy and the early detection of adverse reactions (respiratory depression requiring immediate intervention) [158].

METHODS FOR PAIN INTENSITY ASSESSMENT

In order to monitor one's responses to analgesic treatment and verify its management (if required), the use of validated tools is recommended (scales of postoperative pain assessment (I B, strong recommendation moderate-quality evidence). The tools assessing the severity of pain use various methods of pain measurement (scales: visual-analogue; numerical; verbal). The choice of a scale (tool) should be based on such factors as developmental status, cognitive status, consciousness level, educational level and linguistic differences [159–161].

Examples of the recommended subjective assessment of pain intensity in adults are as follows:

- 5-point numerical rating scale (NRS 0–5) [162],
- 10-point numerical rating scale (NRS 0–10) [163],
- verbal rating scale (VRS) [163],
- visual analogue scale (VAS) (0–10 cm or 0–100 mm) [164].

The assessment of pain intensity should be regularly monitored not only at rest but also in situations that can provoke and intensify pain (which is important and emphasised in the literature), e.g. during post-tonsillectomy swallowing, deep breathing and coughing after a thoracotomy and abdominal procedures, as well as during walking after lower limb surgeries. The pain intensity should not exceed an NRS score of 4 (0–10-point scale); in situations provoking severe pain, up to 6 [165].

If the level of pain severity is high and unresponsive to routine management, it should be evaluated whether the pain does not result from a new condition, postoperative complications or potential tolerance to opioids. The evaluation is to determine which of the interventions is going to be effective, the way pain affects the functional changes, the type of pain (e.g. neuropathic, visceral, somatic, spastic), as well as possible impediments to effective pain treatment (cultural or linguistic differences, intellectual limitations or false beliefs regarding pain management).

There is no sufficient evidence to indicate special recommendations concerning the optimal time and frequency of re-assessment of postoperative patients. The time of assessment after the intervention should correspond to the period in which the maximum efficacy is achieved, most commonly, 15–30 minutes after parenteral pharmacotherapy or 1–2 hours after oral analgesic administration.

MULTIMODAL THERAPY — GENERAL PRINCIPLES

The concept of multimodal (“balanced”) analgesia was introduced for postoperative pain management more than 20 years ago [166]. The method is defined as the use of a variety of analgesic medications and techniques that target many mechanisms of action in the peripheral and/or CNS system (also combined with non-pharmacological interventions) resulting in additive or synergistic effects and more effective pain relief compared with single-modality interventions. The suggested analgesic techniques are based on regional blocks (peripheral or central) in combination with systemic opioids and other analgesics as part of a multimodal approach to postoperative pain management. The use of opioid analgesics may not be required in all patients. One study has suggested that opioids should be avoided when not needed, as there is some evidence demonstrating that perioperative opioid therapy may be associated with an increased risk of prolonged opioid use and the resultant dangers [167].

Randomised trials [168, 169] demonstrate that multimodal analgesia involving the simultaneous use of several combined drugs affecting various receptors, or at least one pharmacological method based on different techniques (e.g. systemic supply and central blocks), is associated with excellent pain relief and reduced requirements for opioids, as compared with a single drug administered using one technique, even after excluding those trials which were retracted due to scientific fraud or those that had not been retracted despite their author having admitted falsifying the data in other studies [170, 171].

For any given situation, there are numerous potential combinations and various multimodal methods that can prove effective depending on the type of surgery, individual clinical factors and patient's preferences. Given the dangers

associated with opioid use, contraindications or planned long-term treatment of postoperative pain, it is recommended to use opioid-free multimodal analgesia based on the simultaneous use of several drugs affecting different receptors in combination with regional techniques [168, 169].

The choice of multimodal therapy is a challenge as many potential combinations can be designed for each surgical procedure, mainly targeted at reducing opioid requirements. However, while using multimodal analgesia, anaesthetists should be aware of the different side effect profile for each analgesic or technique applied. When three or more analgesics are combined, it is difficult to draw explicit conclusions and anticipate the safety and efficacy of such a therapy, due to the diversity of mechanisms of analgesic actions, doses, routes of administration, etc. It is essential to provide suitable monitoring to identify adverse effects and manage them (i.e. to apply effective treatment) [172–174].

Multimodal analgesia for postoperative pain management, targeted at reducing opioid requirements or eliminating them, is strongly recommended (I A strong recommendation, high-quality evidence).

OPIOID ANALGESICS FOR POSTOPERATIVE PAIN THERAPY

In patients in whom the use of opioids for postoperative pain management is required, the enteral route of administration is recommended, provided that there are no contraindications for oral supply (I B strong recommendation, moderate-quality evidence).

The majority of evidence suggests intravenous administration of opioids in postoperative analgesia is not superior to the oral route and is generally preferred [175]. Given the continuous nature of postoperative pain during the first day and the necessity to initially titrate opioids, long-acting opioids are not recommended (due to a lack of evidence proving effective pain control). The exception is patients receiving long-lasting opioids preoperatively.

It is not recommended to use preoperative opioids in order to reduce the severity of postoperative pain or opioid requirements (study findings demonstrate a lack of evident benefits [176, 177]).

The intramuscular supply of analgesics (opioid and non-opioid) for acute and postoperative pain management is not advised (I B strong recommendation, moderate-quality evidence) as it may cause a substantial pain at the site of injection and is associated with unpredictable absorption, which restricts the control of postoperative analgesia [178, 179].

PCA for intravenous opioid administration is recommended and necessary in patients with intestinal obstruction and the risk of aspiration after surgical procedures as they cannot take drugs orally (enterally) (I B strong recommendation, moderate-quality evidence). Intravenous PCA should be used in the group of patients requiring long-term

(at least 24h) opioid analgesia whose cognitive functions are preserved (understanding the functioning of devices and health consequences of this technique, its limitations and safety) [180–182].

The use of single intravenous doses of opioids may be considered in the immediate postoperative period (the first several hours) in order to achieve quick pain relief and to titrate analgesic doses. Single intravenous doses may also be used in patients under sedation, provided that vital functions are strictly monitored [176]. In the immediate postoperative period, intravenous boluses may be considered in order to quickly alleviate pain and suitably titrate the opioid dose. Possible sequels of this method, i.e. increased sedation or respiratory depression, should be monitored [176].

The routine use of basal infusions with i.v. PCA is not recommended, particularly in opioid-naïve adults (I B strong recommendation, moderate-quality evidence) [183, 184].

Additionally, the basal infusion of opioids is associated with an increased risk of nausea and vomiting, as well as respiratory depression [185]. There is still no strong evidence about the usefulness of opioid basal infusion in patients receiving long-term preoperative opioid therapy.

It is recommended to monitor appropriately the depth of sedation, the efficacy of ventilation and other adverse side effects of postoperative opioids (I B strong recommendation, moderate-quality evidence).

Due to the risk of excessive sedation and respiratory depression, patients receiving systemic opioids postoperatively should be strictly monitored during the first post-surgery hours and after dose changes [186]. This monitoring should include an assessment of the degree of sedation and the signs and symptoms of hyperventilation or hypoxia. Although the respiratory system is often postoperatively monitored using pulse oximetry, it is not clear whether this method is superior to the observation of respiratory rates and sedation carried out by nurses; randomised trials have not proven evident effects on clinical outcomes while the sensitivity of pulse oximetry is too low to identify hyperventilation when supplemental oxygen is being administered [187].

Limited evidence suggests that capnography may prove to be more sensitive than pulse oximetry in detecting respiratory depression in patients receiving supplemental oxygen [188]. The evidence is insufficient to explicitly recommend the use of capnography or other more sophisticated methods of monitoring. The risk factors of respiratory depression include a history of sleep apnoea [189] and the use of other CNS-depressive drugs [186].

NON-OPIOID DRUGS FOR ACUTE POSTOPERATIVE PAIN MANAGEMENT

Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended as part of multimodal analgesia unless there

are specific contraindications (IA- strong recommendation, high-quality evidence).

The administration of NSAIDs is associated with an increased risk of gastrointestinal bleeding, cardiologic incidents and kidney dysfunction, which should be considered when choosing treatment. The literature demonstrates that the risk of gastrointestinal disturbances is lower when celecoxib, a selective cyclooxygenase 2 inhibitor, is used. Although animal studies suggest an association between bone non-union after orthopaedic surgeries and NSAIDs, there is no strong evidence confirming the effects of NSAIDs on non-union rates. Although some observations suggest a possible association between high doses of NSAIDs and non-union in spinal fusion [186, 190], this association has not been found to be statistically significant in the analysis of strong-evidence studies. Observational studies suggest that exposure to NSAIDs may be associated with an increased risk of anastomotic leakage after colon surgeries [191–193]. No sufficient evidence has been found to recommend against the use of NSAIDs in patients undergoing surgeries for orthopaedic fractures, spinal fusion and colon procedures. There are contraindications for NSAID use in postoperative pain management in patients undergoing coronary artery bypass grafting procedures due to an increased risk of cardiovascular incidents [194].

It is recommended to administer a preoperative oral dose of celecoxib in adults, unless contraindicated (IB strong recommendation, moderate-quality evidence).

Celecoxib reduces opioid requirements after surgery; moreover, many studies have reported significantly reduced postoperative pain [195–197].

It is recommended to consider the use of gabapentin or pregabalin as a component of multimodal therapy (I B strong recommendation, moderate-quality evidence) in order to reduce postoperative opioid requirements and to achieve the direct analgesic effect [198–200].

It is suggested to supply gabapentinoids, particularly in patients undergoing surgeries associated with substantial pain or as part of multimodal therapy in patients with a high tolerance to opioids. The possible adverse effects include nausea and sedation that is not connected with respiratory depression. Dose reductions are recommended in patients with kidney dysfunction.

Moreover, intravenous ketamine is recommended to be considered as part of multimodal therapy (II B weak recommendation, moderate-quality evidence).

The available study findings have demonstrated that intravenous infusions of ketamine were associated with reduced postoperative requirements for analgesics, compared with a placebo; according to some studies, the supply of this drug was associated with a lower severity of postoperative pain. Intravenous ketamine was also associated with a lower risk of persistent postoperative pain [201–203].

There is no explicit evidence to determine the optimal method of ketamine dosing. A single preoperative dose of 0.5 mg kg⁻¹ is recommended, followed by intraoperative infusion of 10 µg kg⁻¹ min⁻¹ with or without postoperative infusion at a lower dose [204]. The principles of its use should be known and adverse reactions taken into account (hallucinations, nightmares). It is suggested that ketamine should be reserved for extensive surgical procedures, especially in highly opioid-tolerant patients and those in whom non-opioid analgesia is indicated.

Intravenous lidocaine is recommended in adults undergoing open and laparoscopic abdominal procedures, taking into account contraindications (II B weak recommendation, moderate-quality evidence).

Intravenous lidocaine is recommended as part of multimodal perioperative analgesia in abdominal surgeries with the available study findings demonstrating a shorter duration of gastrointestinal motoric dysfunction and better-quality analgesia, as compared with a placebo [205, 206]. In clinical trials, lidocaine was usually administered in a bolus (100–150 mg or 1.5–2.0 mg kg⁻¹), followed by an infusion of 2–3 mg kg⁻¹ h⁻¹ until the completion of surgery. Ultimately, an induction dose of 1.5 mg kg⁻¹ and an intraoperative dose of 2 mg kg⁻¹ h⁻¹ are recommended [207, 208]. The continuation of intravenous infusion in the postoperative period requires further studies.

LOCAL ANALGESIA

Surgical site infiltration with a local anaesthetic is recommended for procedures in which local anaesthetics were proved to be effective (II B weak recommendation, moderate-quality evidence). Subcutaneous and/or intra-articular local anaesthesia of the surgical site has been demonstrated to be an effective element of multimodal analgesia in numerous surgical procedures, including knee replacements, knee arthroscopic procedures, Caesarean sections, laparotomies and haemorrhoid surgeries [209–211].

The use of surgical site local infiltration should be based on evidence showing a benefit in a given surgical procedure. It is essential to have appropriate knowledge concerning the method of infiltration and its range, which differ depending on the surgery and other local anaesthetics used, including those of extended release such as liposomal bupivacaine [212]. Moreover, although data are limited, continuous intra-articular bupivacaine in patients undergoing shoulder procedures can be associated with chondrolysis [213], which suggests caution while using this method.

PERIPHERAL NERVE BLOCKS

Peripheral nerve blocks are recommended as regional analgesia for surgeries in which the evidence shows their efficacy (I A strong recommendation, high-quality evidence).

It has been demonstrated that peripheral blocks are an effective component of multimodal analgesia for postoperative pain management in numerous surgical procedures, including thoracotomy [214], lower limb arthroplasty [215–217] shoulder surgeries [216] and Caesarean sections [218].

A precondition for safe and effective use of peripheral nerve blocks is appropriate knowledge regarding the use of ultrasound imaging and anatomy, as well as the mechanisms of action of local anaesthetics and their adverse effects. Potential motor blocks and the risk of falls should be taken into account. When continuous blocks using elastomeric pumps (which, unlike electronic pumps, are not equipped with an alarm) are decided upon, the patient and/or caregivers should be instructed about the functioning of such a pump and the symptoms of toxic reactions induced by local anaesthetic overdosing.

Continuous methods of peripheral nerve blocks are recommended exclusively when the required duration of analgesia exceeds the time of action of a single injection (I B strong recommendation, moderate-quality evidence).

Both a single injection and continuous peripheral blocks are effective for postoperative analgesia in patients undergoing various surgical procedures [216, 219]. If the duration of postoperative pain is prolonged, continuous blocks are generally preferred to a single injection whose action is limited.

CENTRAL BLOCKS

Central blocks are recommended for postoperative analgesia after thoracic and abdominal surgeries, particularly in patients at high risk of cardiac and pulmonary complications and prolonged ileus (I A strong recommendation, high-quality evidence) [214, 220].

As far as the preventive effect is concerned, there are data demonstrating the efficacy of central blocks in chronic postoperative pain. In order to prevent chronic postoperative pain, it is recommended to use epidural anaesthesia after a thoracotomy and paravertebral anaesthesia for mastectomies [221]. The decision to use epidural analgesia for postoperative pain management has to be associated with numerous factors, while the medical personnel should consider the risk-benefit ratio. Moreover, adequate monitoring of patients should be provided (I B strong recommendation, moderate-quality evidence).

Although epidural analgesia is associated with a lower risk of perioperative mortality, as well as cardiac and pulmonary complications, as compared with systemic opioids, the adverse effects and complications of this method should be taken into account (respiratory depression, hypotension, epidural haematoma or abscess) [214]. In patients undergoing hip or lower extremity surgical procedures, central blocks may mask the symptoms of tunnel syndrome. Due

to the above-mentioned effects of central blocks, patients should be monitored and the attending personnel should be prepared to implement the methods for the prevention and treatment of adverse effects and complications (reduction in drug doses, catheter removal in cases of haematomas or abscesses) or to undertake some other measures, as required.

PAIN CONTROL TEAMS — STRUCTURE AND FUNCTIONING

The centres in which surgical procedures are performed are recommended to have an organisational structure (or re-organise the existing one) in order to develop and improve the management policy of safe and effective postoperative pain relief (I C strong recommendation, low-quality evidence).

The centres in which surgical procedures are performed should have an organisational structure in order to oversee the development, implementation and assessment of principles and practices in order to assure safe, evidence-based and effective postoperative pain control. Ideally, the process should be interdisciplinary, provided by already existing organs or a designated pain control team. The role of administrative and medical management is emphasised, including the units that are most integrally connected with perioperative pain management. Access to specialist consultations should be provided for patients with inadequate postoperative pain management or those at high risk of inadequate postoperative pain management (e.g. a history of opioid tolerance or dependence or chronic pain) (I C strong recommendation, low-quality evidence).

Postoperative pain treatment can be a challenge and requires the advanced methods of assessment and management skills that specialists in pain therapy possess. In some cases, postoperative pain may be controlled inadequately despite the use of standard multimodal therapies [222].

Centres using advanced techniques of central and peripheral blocks should have appropriately educated personnel and ensure training, supervision and the gaining of experience in order to assure safe and effective treatment. Those centres employing advanced techniques of postoperative analgesia should have clearly defined policies and procedures ensuring the adequate monitoring of patients and competent, well-trained and educated personnel involved in caring for these patients. Moreover, clear and reliable principles for hospital and nursing staff to be able to contact specialists employing the above-mentioned techniques should be defined (I C strong recommendation, low-quality evidence).

POST-HOSPITAL POSTOPERATIVE PAIN CONTROL

It is recommended that physicians provide both patients (or legal guardians) and staff ensuring basic health care with information regarding pain therapy plans, including the

gradual reduction of analgesic doses after discharge (I C strong recommendation, low-quality evidence).

Studies on the methods and outcomes of discharge planning are few and insufficient to recommend particular optimal methods [223]. Nevertheless, the available reports and clinical experience suggest the need for proper coordination of actions after discharge, as part of a postoperative pain management plan. A coordinated approach to recommendations after discharge is highly important, including advice and support from family doctors, nurses, physiotherapists and pharmacists [224].

DETAILED RECOMMENDATION — ANALGESIC MANAGEMENT IN SELECTED TYPES OF SURGERIES

The recommendations do not include doses of individual drugs (they should be used in accordance with the Summary of Product Characteristics or the suggestions of the authors presented in the remaining chapters of the recommendations, based on the 2014 guidelines which described the doses of all drugs in detail).

ARTHROSCOPIES, ENDOSCOPIC UROLOGICAL PROCEDURES, SKIN AND SUBCUTANEOUS TISSUE PROCEDURES

- paracetamol and/or
- nonsteroidal anti-inflammatory drugs (NSAIDs):
 - a) coxibs or
 - b) selective NSAIDs: nimesulide, meloxicam or
 - c) non-selective NSAIDs (diclofenac, or ibuprofen or ketoprofen or dexketoprofen)
- and/or
- d) metamizole and /or
- e) tramadol (capsules, drops).

All the above analgesics are recommended for oral administration. During the following postoperative days, the number of drugs should be gradually reduced (without reducing the doses), taking into account the severity of pain reported by the patient.

Techniques of local analgesia:

- adductor canal block (knee arthroscopy, 20 mL 2% lidocaine or 20 mL 0.375% ropivacaine or 0.375–0.25% bupivacaine);
- brachial plexus block (shoulder arthroscopy, 10–15 mL 2% lidocaine or 0.375–0.5% ropivacaine or 0.375–0.5% bupivacaine) or
- axillary and suprascapular nerve block (shoulder arthroscopy, 5–10 mL per each nerve, 2% lidocaine, or 0.375% ropivacaine, or 0.25% bupivacaine);
- surgical incision injection with a local anaesthetic (1–2% lidocaine, 0.2% ropivacaine, 0.125–0.25% bupivacaine, in a volume dependent on the extent of the incision, and not exceeding maximum doses).

LAPAROSCOPIC CHOLECYSTECTOMY, APPENDECTOMY, INGUINAL HERNIA REPAIR, STRUMECTOMY

Before surgery:

- nonsteroidal anti-inflammatory drugs (NSAIDs):
 - a) coxibs (B) or
 - b) selective NSAIDs: nimesulide, meloxicam (*p.o.*) (C) or
 - c) non-selective NSAIDs (diclofenac or ibuprofen or ketoprofen or dexketoprofen) (*p.o.*) (A);
- dexamethasone (*i.v.*) (B);
- gabapentin (*p.o.*) (B);
- lidocaine (*i.v.*) (B).

Local techniques:

- ilioinguinal and iliohypogastric nerve block (B) (10–15 mL of local anaesthetics, e.g. 0.2% ropivacaine, or 1–2% lidocaine, 0.1–0.125% bupivacaine) or
- incision site infiltration 0.25–0.5% ropivacaine 30–40 mL or 0.25–0.5% bupivacaine up to 30 mL (A) or
- quadratus lumborum block (QLB) (15–20 mL), 0.2% bupivacaine or 0.375% ropivacaine (C) (inguinal hernia repair, traditional method);
- trocar site injection with local anaesthetics (LAs) (A) (laparoscopic procedures);
- incision site injection with LAs (0.25–0.5% ropivacaine 10–20 mL, 0.25–0.5% bupivacaine 10–20 mL) (A) (strumectomy).

After surgery:

- paracetamol and/or metamizole (A) and/or
- NSAIDs (ketoprofen or dexketoprofen or coxibs [no contraindication and possible oral administration]) (A);
- weak opioids (C) — tramadol;
- strong opioids (morphine, oxycodone) as rescue analgesia (C) [225].

In cases of high risk of pulmonary complications, thoracic epidural analgesia is recommended (laparoscopic cholecystectomy) (B).

Parenteral postoperative analgesia should be replaced with non-invasive methods of administration (enteral) as quickly as possible; opioids should be replaced with non-opioid analgesics and the intensity of pain ought to be regularly controlled.

TONSILLECTOMY

Before surgery:

- nonsteroidal anti-inflammatory drugs:
 - a) coxibs (B) or
 - b) selective NSAIDs: nimesulide (*p.o.*) (C) or
 - c) non-selective NSAIDs (ibuprofen) (*p.o.*) (C);
- dexamethasone (*i.v.*) (B);
- gabapentin (*p.o.*) (C).

After surgery:

- paracetamol and/or metamizole (A);
- and/or NSAIDs (ketoprofen or dexketoprofen or coxibs [no contraindication and possible oral administration]) (A);

- weak opioids (C) (tramadol);
- strong opioids (morphine, oxycodone) as rescue analgesia (C).

Local techniques:

- post-tonsillectomy site injection 5–7 mL per side: 0.25–0.375% bupivacaine or 0.5% ropivacaine, or 2% lidocaine [227–231].

CAESAREAN SECTION

Before surgery:

- gabapentin (*p.o.*) (I A);
- dexamethasone (*i.v.*) (II B).

After surgery:

- paracetamol (*i.v.*) (I A);
- morphine (*i.v.*) (PCA) (I A);
- or nalbuphine (*i.v.*) (PCA) (II B).

Local analgesia:

- quadratus lumborum block (QLB) (15–20 mL per side), 0.2% bupivacaine or 0.375% ropivacaine (C) or
- transversus abdominis plane (TAP) block, 15–20 mL per side 0.125–0.25% bupivacaine or 0.2–0.375% ropivacaine (C) or
- wound injection or continuous infiltration with LAs (IA) [231–234].

MASTECTOMY

Before surgery:

- paravertebral block (paravertebral blockade — PVB) (A);
- pectoral nerve blocks PECS 1 PECS 2 (pectoral nerve blocks 1, 2) 10–20 mL 0.2% ropivacaine or 0.1% bupivacaine, serratus anterior plane block (SAPB 1, 2);
- gabapentin (*p.o.*) (A);
- coxibs (*p.o.*) (C);
- paracetamol (*p.o.*) (B).

After surgery:

- (VAS > 5) NSAIDs or coxibs (A) + paracetamol (B) + strong opioids (B) and/or metamizole;
- (VAS > 3 < 5) NSAIDs or (A) + paracetamol (B) + weak opioids (B) and/or metamizole.

Local analgesia:

- continuation of continuous PVB analgesia (A) or continuous thoracic segmental blocks (C) [235–237].

THORACOTOMY

Before surgery:

- thoracic epidural anaesthesia/analgesia (TEA) with LA + strong opioid (A) or
- paravertebral block (PVB) with LA (A) or
- intercostal block (C) or
- one of the thoracic peripheral blocks (QLB or ESP or PECS 1 and 2) (C);

- phrenic nerve block (C) (prevents and relieves shoulder pain);
- incision site infiltration with LA (A).

After surgery:

- TEA continuation (continuous infusion or PCA) (A) or
- PVB continuation (continuous infusion PCA) (A) or
- systemic analgesia (no possibility to perform or lack of efficacy of regional analgesia);
 - a) non-selective NSAIDs (*i.v.*) (A) or
 - b) coxibs (*p.o.*) (B);
 - c) strong opioids (*i.v.* PCA) (A) + NSAID (A) + paracetamol (A) or
 - d) weak opioids (*i.v.*) (C) + NLPZ + metamizole + paracetamol [238–241].

LAPAROTOMY

Before surgery:

- coxibs (*p.o.*) (B);
- lidocaine (*i.v.*) (B);
- thoracic epidural anaesthesia (PCA) (A) or
- bilateral TAP block (15–20 mL per side 0.125–0.25% bupivacaine or 0.2–0.375% ropivacaine (C) or
- bilateral QLB (15–20 mL per side, 0.2% bupivacaine or 0.375% ropivacaine) (C) or
- before closure of integuments — injection or supraperitoneal continuous infiltration (B).

After surgery:

- TEA continuation (A) or
- NSAID (*i.v.*) (A) + lidocaine (*i.v.*) (B) + strong opioid (*i.v.* PCA) (B) or
- NSAID (*i.v.*) (A) + lidocaine (*i.v.*) (B) + weak opioid (*i.v.*) (B) + paracetamol (*i.v.*) (B) + metamizole (*i.v.*) (B) [242].

RADICAL PROSTATECTOMY

Before surgery:

- coxibs (B);
- gabapentin (B);
- dexamethasone (B);
- lidocaine (*i.v.*) (C).

After surgery:

- local analgesia: incision line injection with LA (B);
- coxibs (*p.o.*) (B);
- lidocaine (*i.v.*) (B);
- strong opioids (*i.v.* PCA) (B) + coxibs (C) + paracetamol (*i.v.*) (C) or
- weak opioids (*i.v.*) (B) + paracetamol (*i.v.*) (B) + metamizole (*i.v.*) (B).

HIP PROSTHEOPLASTY

Before surgery:

- lumbar epidural analgesia (LEA) only in patients at high risk of pulmonary complications;

- subarachnoid anaesthesia with LA + opioid (A) or fascia iliaca peripheral blocks(A).

After surgery:

- continuation of LEA or
- coxibs (*p.o.*) (A) or
- NSAID (*i.v.* or *p.o.*) (B) + strong opioids (*i.v.* PCA) (B) + paracetamol (*i.v.* or *p.o.*) (A) or
- NSAID (*p.o.*) (B) + weak opioids (*p.o.* or *i.v.*) (B) + paracetamol (*i.v.* or *p.o.*) (A) + metamizole (*i.v.* or *p.o.*) (B).

KNEE PROSTHEOPLASTY

Before surgery:

- general anaesthesia + continuous femoral nerve or adductor canal block (A);
- subarachnoid anaesthesia + femoral nerve or adductor canal continuous block(A);
- dexamethasone (*i.v.*) (C);
- gabapentin (*p.o.*) (C);
- ketamine (*i.v.* 0.25–0.5 mg kg⁻¹) (C).

After surgery:

- continuation of peripheral continuous block (continuous infusion or PCA);
- NSAID (coxibs) (A);
- strong opioids (*i.v.* PCA) (A) + paracetamol (*i.v.* or *p.o.*) (B);
- weak opioids (*i.v.* or PCA) + paracetamol (*i.v.* or *p.o.*) (B) + metamizole (*i.v.* or *p.o.*) (C) [243–246].

ANORECTAL PROCEDURES

Before surgery:

- gabapentin (*p.o.*) (C);
- ketamine (*i.v.*) (C);
- subarachnoid anaesthesia with LA + opioid or
- perirectal infiltration with LA (e.g. 0.25–0.5% ropivacaine, 30–40 mL or 0.25–0.375% bupivacaine up to 30 mL) (A) or
- pudendal nerve block (A).

After surgery:

- NSAIDs (coxibs) + paracetamol + strong opioids (B) or
- NSAIDs (coxibs) + weak opioids + metamizole (B).

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