Jiří Málek, Pavel Ševčík, et al.

Postoperative Pain Management

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1 Introduction

Acute pain is one of the most common symptoms, for which physicians are consulted. It is a symptom informing the organism about tissue insult (caused by injury, disease, surgical procedure, or childbirth) in order to prevent further damage. Acute pain is an unpleasant sensory, emotional and mental sensation (experience) associated with vegetative signs, psychological response and changes in behavior. It usually lasts for several hours to days, rarely more than a month. Acute pain makes the patient seek medical help within minutes, hours or a few days after the onset of pain. If this signal is ignored, pain may become chronic. Acute pain is provoked by identifiable stimuli and disappears as soon as the tissue injury or damage that had caused it is healed.
Postoperative pain is a typical example of acute pain. All surgical procedures are associated with a certain level of postoperative pain. Fear of postoperative pain is one of the greatest concerns of patients undergoing surgery. A number of studies conducted in countries with a highly-developed health care system demonstrated that even in the first decade of the 21st century, postoperative pain was not managed well in one-third to one-half of patients. Yet it seems that there is some kind of progress over time. In the Czech Republic, for example, in epidemiological studies conducted by J. Málek et al. in 2006, 18.5% of patients considered pain to be the worst experience in the postoperative period and in 36% of cases pain was an important source of complaints after surgery. In 2014, the study was repeated at the same department (the results have not been published yet) and revealed that less than 20% of respondents suffered from severe pain, none of the patients reported excruciating pain and 6 hours after surgery the incidence of severe pain fell below 10%. A secondary finding in both studies is that the patients themselves do not attach such importance to postoperative pain – only 5% of them were not satisfied with the treatment. Despite the recent progress, there is still potential for further improvement of analgesic therapy. We would like to emphasize that untreated postoperative pain is a highly preventable issue, which can easily be solved. Nowadays, there is an abundance of medications, dosage forms, acute pain management techniques, and ample data on postoperative pain treatment. The main challenge is to translate this knowledge into everyday practice. Possible reasons for the inadequate postoperative pain management include limited financial resources, lack of time and personnel, but also reluctance to address this issue, organizational

aspects of the health care facility, and lack of simple and clear guidelines for the treatment of postoperative pain. Providing such easy-to-follow recommendations is one of the objectives of this book. The availability of postoperative analgesia to anyone who needs it requires a high-quality postoperative pain management, as well as accepting and understanding the fact that good analgesia is not only necessary, but also a fundamental right of every patient suffering from pain and a basic duty of any health care facility that treats these patients. In addition to this ethical point of view, there are other medical and economical aspects associated with a frequently reported reduced morbidity, more rapid recovery and discharge of the patient from hospital.

2

Pathophysiology of acute postoperative pain

2.1 General remarks

Pain is characterized by four basic components, which also define its manifestation:
– **sensory-discriminative component**
– **affective (emotional) component**
– **vegetative (autonomic) component**
– **motor component**

Acute pain is usually easy to locate. The organism responds to pain with physiological changes, which are basically identical to changes during the stress response. High-intensity acute pain is a major psychological burden. Causal treatment together with an effective symptomatic analgesic therapy usually alleviates acute pain. If an effective analgesic therapy is initiated early on during the acute phase of pain, the risk of progression to chronic stage is greatly reduced. An example may be an early initiation of analgesic therapy as a prevention of postherpetic neuralgia.

Acute pain is a major stressor triggering **neuroendocrine, immune, and inflammatory response** (psycho-neuro-endocrino-immunological changes). This leads to an increased level of certain (stress) hormones, catabolism with tissue loss, immunosuppression, increased myocardial oxygen consumption due to tachycardia and increased cardiac output, greater susceptibility to thromboembolism, vasoconstriction, decreased GI motility, deterioration of lung functions, and, as a result, increased morbidity and mortality. Excessive stress is provoked not only by the pain itself, but also by the actual illness, injury, or surgical procedure. Thus, a **synergic causal and symptomatic solution** is necessary to reduce the stress response and ultimately morbidity and mortality. Early and sufficient analgesia facilitates early mobilization and discharge from hospital to outpatient care and reduces postoperative complications.

Acute pain usually causes only short-term psychological changes. Most patients will temporarily experience concern or fear. The extent of these changes may be reduced by proper previous **psychological preparation and interview** within the preoperative preparation. The cause and duration of acute pain significantly affect the type and extent of psychological changes. The clearer the cause and mechanism of pain, the better the pain and its consequences are processed and dealt with by the patient.

The perception and response to acute pain is greatly influenced by our genetic composition, cultural and social background, age, and gender. Certain groups of patients are at a higher risk of inadequate pain management and require special attention, namely children, geriatric patients and patients with communication problems (critical state, cognitive disorders, language barriers).

2.2 Pathophysiology of postoperative pain

2.2.1 Formation of reflexes in postoperative pain

Postoperative pain is a model case of acute pain both from pathophysiological and therapeutic point of view. Surgical procedure causes local tissue damage, resulting in the release of prostaglandins, histamine, serotonin, bradykinin, substance P, and other mediators, production of noxious stimuli, and irritation of free nerve endings and nociceptors (**nociceptor pain**). Bradykinin, serotonin and histamine both sensitize and stimulate the receptors, arachidonic acid metabolites only sensitize them. Pain may also arise directly in peripheral or central neural structures, if they suffer damage during the surgical procedure (**neuropathic pain**).

Pain signals are transmitted by thinly myelinated A-delta fibers and unmyelinated C fibers of primary afferent neurons into the central nervous system. In the spinal cord, they are modulated in a complex way and some of them are transferred to anterior horns and provoke segmental reflex responses. Others are passed upwards via the spinothalamic and spinoreticular tracts and provoke suprasegmental and cortical responses. Autonomic nerves are also involved in the transfer of pain signals.

Postoperative pain may originate in skin, or deeper somatic and visceral structures. It can be divided into nociceptive somatic (from skin, muscles, bones), nociceptive visceral (from organs of the thoracic and abdominal cavity), and neuropathic (caused by damage to neural structures). Usually it is a combination of several types of pain.

Segmental reflexes cause increased tension and spasms of skeletal muscles, thereby increasing oxygen consumption in the muscles and lactate production. Stimulation of sympathetic neurons produces tachycardia, increase in stroke volume, cardiac work, myocardial oxygen consumption, decrease in smooth muscle tone in the GI and urinary tract.

Suprasegmental reflexes further increase sympathetic nervous system tone and stimulate hypothalamus and the hypothalamic–pituitary–adrenal axis. Metabolic rate increases, mainly catabolism and myocardial oxygen consumption.

Cortical responses are caused by the activation of complex systems associated with the integration and perception of pain. Pain may be accompanied by concern and fear, which further stimulate hypothalamus.

2.2.2 Negative effects of postoperative pain on various organ systems

Pathophysiological response to tissue damage and stress is characterized by pulmonary, cardiovascular, gastrointestinal and urinary dysfunction, impaired muscle metabolism and function, neuroendocrine, immune and metabolic changes. Most of these effects may be mitigated by analgesic therapeutic procedures.

Changes in respiratory functions. Surgical procedures of the epigastrium and chest reduce vital capacity (VC), functional residual capacity (FRC), tidal volume (VT), residual volume (RV), and forced expiratory volume in one second (FEV1). As a reflex response, abdominal muscle tone increases and diaphragm function is limited. This results in reduced lung compliance, muscle stiffness, inability to breathe deeply and expectorate. In more advanced cases, this is followed by hypoxemia, hypercapnia, retention of secretions, atelectasis, and pneumonia. An increased muscle tone contributes to increased oxygen consumption and lactate production. Dilated bowel due to postoperative ileus or an overly tight bandage may further restrict ventilation. The patient is afraid to breathe deeply and expectorate out of fear that it might provoke pain.

Cardiovascular changes. Sympathetic stimulation causes tachycardia, increase in stroke volume, cardiac work, and myocardial oxygen consumption. In susceptible individuals, this leads to an increased risk of ischemia, or even myocardial infarction. The patient restricts physical activity out of fear of pain, which is followed by venous stasis, subsequent platelet aggregation, possible venous thrombosis and venous thromboembolism (VTE).

Gastrointestinal and urinary changes. Typical changes associated with postoperative condition and pain include intestinal hypomotility, or even paralysis, nausea, vomiting, hypomotility of ureters and bladder, which can result in problems with urination. Opioid analgesia may also contribute to these symptoms. However, this must not be an argument against properly performed analgesia.

Neuroendocrine and metabolic changes. Suprasegmental reflex responses increase sympathetic tone, stimulate the hypothalamus, increase the production of catecholamines and catabolic hormones (cortisone, adrenocorticotropic hormone - ACTH, antidiuretic hormone - ADH, growth hormone, glucagon, aldosterone, renin, angiotensin II) and reduce the secretion of anabolic hormones (insulin, testosterone). This leads to sodium and water retention, increase in blood glucose, free fatty acids, ketone bodies, and lactate. Metabolism and oxygen consumption increase and metabolic substrates are mobilized from stores. If this process continues, catabolic state and negative nitrogen balance result.

2.2.3 Psychological effects of postoperative pain

Acute pain may produce fear and anxiety, followed by anger, resentment, and negative relationship with physicians and nurses. Pain induces or exacerbates insomnia, which further hinders mental and physical recovery.

2.2.4 Late effects of insufficient postoperative analgesia

Besides short-term **negative effects on various organ systems** (see above), **postoperative pain** also has many long-term effects. Of these, **chronic postoperative pain** is the best-known effect. In children, undermanaged postoperative pain might lead to a prolonged (up to 1 year) **risk of changes in behavior**.

Chronic postoperative pain

The phenomenon of chronic postoperative pain started to receive attention only in the 1990s. Chronic postoperative pain occurs in connection with a surgical procedure and persists longer than the usual time of healing, which is usually limited to 3 months (or up to 6 months according to some authors) after the procedure. Long-term moni-

toring of patients following a surgical procedure revealed that the incidence of chronic pain is surprisingly common. The best-known example is phantom pain after limb amputation, followed by chronic postoperative pain after thoracotomy, breast surgery, cesarean section, or inguinal hernia repair, which is associated with pain during intercourse in 1% of patients, mainly men. Chronic postoperative pain is more likely to develop in younger people, in individuals already suffering from intense pain before surgery and in patients with severe acute postoperative pain. In addition, it might be influenced by the surgical approach and possibly by the anesthetic procedure. The problem is that results vary across the different types of surgical procedures, as well as across studies on the same type of procedure. The current view is that genetic factors play a central role and influence nociceptive and antinociceptive endogenous systems, since both intense acute perioperative pain and the risk of developing chronic postoperative pain may be affected by this mechanism.

The pathophysiology behind chronic postoperative pain is better known. Following a surgical trauma, the injury site releases inflammatory mediators, which sensitize the surrounding nociceptors and lower the threshold for generating impulse at the injury site and in surrounding tissues. Simultaneously, the primary neuron of the pain pathway releases substances into the area around peripheral nerve endings, which contribute to this process – this results in peripheral sensitization. Other changes take place at the level of spinal cord neurons. If the C fibers permanently transmit signals from the painful area to the central nervous system (firing), neurons in the spinal dorsal horns enhance their response, their receptive area expands and the number of spinal receptors stimulating nociceptive pathways increases, which produces central sensitization (= lowering the threshold for response to other stimuli). This leads to hyperalgesia – an increased pain response to a normally painful stimulus, and allodynia – a painful response to a normally innocuous stimulus. Furthermore, a remapping of sensory areas in the brain occurs. It is not yet clear, however, why some patients are caught in this vicious circle resulting in postoperative pain chronification, and others are not. Sometimes it is caused by peripheral nerve injury or by a sustained stimulation of nociceptors by a scar. Nevertheless, in many clinical cases, the underlying cause is not clear.

Currently, the identification of a high-risk patient may be based solely on the presence of predisposing factors. A clinical study proved that the incidence of neurogenic pain and the size of the hyperalgesic area around the surgical wound measured on the second and third postoperative day are predisposing factors for chronic postoperative pain. However, the impact of this finding on the common clinical practice is difficult to estimate at this stage.

At the current state of knowledge, the possibilities for prevention are very limited. Even as obvious methods at first glance as limiting the extent of surgical trauma did not produce definite results. Based on the information that chronic pain is related to intense perioperative pain, much hope was pinned on preemptive analgesia – the administration of medications inhibiting primary and central sensitization before they might occur, i.e. before the surgical procedure. This hope was further strengthened by positive results achieved in animal models. Unfortunately, in human medicine, the results were not clearly positive and following the information boom at the turn of this century, studies on preemptive analgesia are becoming less frequent (see section 6.5). Similar controversial conclusions are drawn in studies on the importance of locoregional methods in comparison with general anesthesia or a combination of local and general anesthesia compared to general anesthesia alone. Methods using locoregional techniques have been shown to improve various factors, including analgesia, for up to 10 days after surgery. However, long-term results have shown no effect. The same conclusion was reached in our study monitoring, among other things, the influence of continuous thoracic epidural analgesia versus systemic analgesia on the incidence of chronic pain after sternotomy.

Table 2.1 Incidence (in percent) of chronic postoperative pain (modified according to Macrae WA, 2001)

Surgical procedure	%	Surgical procedure	%
Amputation	30–85	Spongioplasty	30
Thoracotomy	5–67	Total hip replacement	28
Mastectomy	11–57	Varicose vein stripping	27
Inguinal hernia	0–63	Hysterectomy	25
Sternotomy	28–56	Craniotomy	6–23
Cholecystectomy	3–56	Abdominoperineal resection	12–18
Total knee replacement	19–43	Cesarean section	12
Breast augmentation	13–38	Dental surgery	5–13
Gyn. laparotomy	32	Vasectomy	0–37
Prostatectomy	35	Painful ejaculation after inguinal hernia repair	1

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3

Factors affecting postoperative pain

The intensity, quality and duration of postoperative pain is affected mainly by:

- location, type, and duration of the surgical procedure
- type and extent of the incision and surgical trauma
- physical and mental state of the patient including the patient's personal approach to pain
- preoperative psychological and pharmacological preparation
- type of anesthesia
- pain management before and after the surgical procedure
- incidence of surgical complications
- quality of postoperative care

The first two factors mentioned affect postoperative pain as follows:

- **Severe pain lasting more than 48 hours** is caused by extensive surgical procedures in the epigastrium, thoracic surgery, surgery of the kidneys, hemorrhoids, and rectum, surgery of major joints and bones with the exception of hips, spinal surgery.
- **Severe pain lasting less than 48 hours** is caused by cholecystectomy, prostatectomy, abdominal hysterectomy, and cesarean section.
- **Moderate pain lasting more than 48 hours** is caused by heart surgery, hip surgery, surgery of the larynx and pharynx.
- **Moderate pain of shorter duration** is caused by appendectomy, inguinal hernia repair, vaginal hysterectomy, mastectomy, intervertebral disc surgery.
- **Mild pain** is, for example, caused by minor gynecological procedures.

Improving analgesia alone may not be sufficient to reduce stress response to surgery. We must also **influence other physiological processes and restore homeostasis**, which will in turn shorten the length of hospital stay, reduce morbidity and mortality. Postoperative analgesia must go hand in hand with **rigorous rehabilitation**.

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4

Pain assessment

In order to treat pain effectively, pain needs to be properly diagnosed, measured and documented. Only then optimal analgesia may be achieved, which is a mild, tolerable sensation of pressure in the surgical wound with minimal adverse effects.

4.1 Diagnosing pain

Proper diagnosis of the type and intensity of pain is crucial for an adequate and targeted treatment of acute pain. It requires a highly professional approach in terms of expertise, psychology, and ethics. The patient should feel sufficient empathy on the part of health care professionals. The examination of acute pain should include medical history, physical examination, and specific evaluation of pain.

When taking a **patient's history**, our focus is on the cause and circumstances of the onset of pain, speed of onset, location, radiation, quality of the pain, and accompanying symptoms (nausea, vomiting, tremor, sweating, etc.). The current treatment of pain and its effect is also evaluated. The type and extent of surgical trauma, the type of anesthesia, the quality of postoperative care, and the incidence of complications play a key role in postoperative pain management. During **physical examination**, we focus on the site of maximum tenderness, but also on distant structures, which may be associated with the pain.

Specific evaluation of pain includes:
a) location of the pain and its radiation
b) quality of the pain – dull, sharp, throbbing, shooting, burning, etc.
c) duration of the pain – constant, intermittent, paroxysmal
d) causative factors – movement, sitting position, cough, etc.
e) intensity of the pain at rest, during movement
f) accompanying symptoms
g) quality of sleep
h) assessment of the patient's expectations, personal approach to pain, stress and pain coping strategies, analgesic therapy preferences

At the end of the examination, we establish the type of pain (nociceptive, neuropathic, visceral, mixed), cause of the pain, if possible, pain intensity and propose an analgesic treatment strategy. In acute postoperative pain, the process can be greatly simplified.

4.2 Measuring pain

Pain is an individual and subjective experience, influenced by various physiological and psychological factors, education, prognosis, sleep deprivation, race, gender, and environmental influences.

Objective methods of measuring pain are used more in experimental medicine, and, above all, in chronic pain management (algometer, tail flick test, plantar test, changes in the level of ROS, cholesterol or blood glucose levels). Measuring physiological changes (heart rhythm), response to stress (plasma cortisol), or changes in behavior (facial expression) can provide important information on the intensity of pain. Other methods of measuring pain are **subjective**.

4.2.1 Nonverbal methods of pain assessment

The most widely used method of numerical assessment of pain intensity is the **visual analogue scale** (VAS), where patients specify the intensity of pain by indicating a point along a continuous horizontal line, with numbers from 0 to 10 on the other side. In Numeric Rating Scale (NRS) the patient uses numbers to quantify the intensity of pain – 0 means no pain and 10 corresponds to the worst pain imaginable. In the elderly, NRS is superior to VAS, as these patients understand the numerical scale better. Pain intensity should not exceed VAS/NRS 3, as VAS 4 needs to be treated.

Pain assessment is also performed with respect to the movement of the patient –VAS score often increases with movement, depending on the range of motion. VAS is also used to evaluate the efficacy of treatment (e.g. 5/2 means 5 before treatment and 2 after treatment; or for example 7/4/2).

An alternative to numerical scale may be an expanding color circle sector or **Faces Pain Scale**, which shows facial expressions ranging from the state of well-being to worst pain possible. This scale is preferred in young children, who are not able to accurately describe or quantify the intensity of pain. Acute pain should be routinely monitored in intensive care as well. In non-cooperative, critically ill patients, Behavioral Pain Scale or Critical-Care Pain Observation Tool are recommended. Monitoring pain by observing changes in vital signs is not recommended.

4.2.2 Verbal methods of pain assessment

These methods use verbal expression to assess the intensity of pain. They allow simple and quick assessment of pain in the elderly, disoriented patients, blind patients, and some children. The most widely used scale is **Present Pain Intensity (PPI):**
0 – none, 1 – mild, 2 – discomforting, 3 – distressing, 4 – horrible, 5 – excruciating.

4.2.3 Multidimensional methods of pain assessment

These methods evaluate not only the intensity, but also the character or quality of the pain and its impact on the affective assessment of pain by the patient. There are many

questionnaires available, the most widely used worldwide is the Short-form McGill Pain Questionnaire – SF-MPQ. These questionnaires are not routinely used in the assessment of acute postoperative pain.

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5

Incidence and intensity of postoperative pain

Most papers on postoperative pain begin by stating that, despite all available information and recommendations for the treatment of acute postoperative pain, there is still a high percentage of patients suffering from severe postoperative pain. The percentage is estimated at between 30 and 40%. It is a well-known fact that there are differences in experiencing pain among various populations due to different genetics, as well as social and cultural background. Therefore, the results of these studies cannot be easily applied to countries with different conditions and traditions. For example, in the Czech Republic, one of the two earlier pilot studies carried out by the author has shown that, although patients felt less fear before surgery (35.5% had no fear) and attached less importance to severe postoperative pain than reported by other authors (only 10% of respondents expressed fear of postoperative pain, the greatest concern (22.5%) was the surgical procedure itself, possibility of malignant disease and the final outcome of the procedure, followed by fear of anesthesia – 18.5%), pain was the worst real experience on the second postoperative day (18.5% of respondents). In the second study, pain was the cause of significant negative experience after surgery in 36% of patients (in descending order: 51.5% drowsiness, 50.7% dry throat, 49% nausea, 47.1% fatigue, 36% pain, 27.2% vomiting). In both studies, higher intensity of pain was reported by women. According to a very recent study conducted at the same department (the results have not been published yet), there has been an improvement: severe postoperative pain was reported by less than 20% of respondents, none of them reported excruciating pain and 6 hours after surgery the incidence of severe pain fell below 10%. Intense pain immediately after surgery was a predictor of severe postoperative pain, which highlights the role of the anesthesiologist in the prevention of severe postoperative pain.

It should be noted, however, that patient satisfaction with postoperative care itself is not a guarantee of adequate analgesia. The paradox that even patients with severe postoperative pain expressed satisfaction with the treatment has been repeatedly reported. This is corroborated by the results of our two studies: only 7.7% and 3.7% of the patients, respectively, were not satisfied with postoperative pain management. The reason for this is that patient satisfaction with postoperative pain management is a

multifactorial experience, and the actual average intensity of pain is only one part of it. The key factor in patient satisfaction is that the surgery went well, and no serious complications occurred. The empathy of nursing staff, time which the patients had to wait before the administration of analgesics, and the speed of onset of action also play an important role. In retrospect, patients tend to evaluate more recent experiences rather than those which occurred immediately after surgery. To sum up, patients tend to erase unpleasant memories. In the second study, we also focused on the maximum intensity of pain our patients are able to tolerate before they ask for analgesics. In the literature, 4 on a scale from 0 to 10, with 0 indicating no pain and 10 reflecting the worst possible pain, is generally considered the cut-off point to start treatment. On average, patients reported the intensity of 5.3 in the entire group, as well as after excluding those with postoperative pain <2, or after including only those with pain intensity >4. Since this was the value of maximum tolerable pain and since the effect of treatment is often not immediate, it is recommended, based on these results, that the value 4 should be an indication to start analgesic therapy and should not be exceeded for an extended period of time.

Finally, it should be emphasized that high-quality postoperative analgesia is not the "holy grail" of postoperative care, but only one of the constituents of patient care after surgery. Relieving anxiety, physical factors (warmth and light comfort after surgery), early initiation of oral intake, fast track surgery or ambulatory surgery and many other factors, which are not always taken into consideration, also play a major role.

Table 5.1 Intensity of pain after various surgical procedures

Surgical procedure	Type of pain	Intensity of pain
Head and neck		
Eye surgery	Nociceptive, neuropathic – enucleation and retinal surgery	Mild to severe
Craniotomy	Nociceptive	Mild to moderate
Extensive ENT surgery	Nociceptive and neuropathic	Moderate to severe
Oro-maxillo-facial	Nociceptive and neuropathic	Mild to severe
Chest (except for cardiac surgery)		
Thoracotomy	Nociceptive and neuropathic Risk of chronic postoperative pain	Moderate to severe
Mastectomy	Nociceptive and neuropathic Risk of chronic postoperative pain	Moderate to severe
Cardiac surgery		
CABG	Nociceptive	Moderate to severe
MID-CAB	Nociceptive	Mild to moderate
Upper abdomen		
Laparotomy	Nociceptive (somatic and visceral) and neuropathic	Moderate to severe
Laparoscopic cholecystectomy	Nociceptive (somatic and visceral) and neuropathic	Mild to moderate
Nephrectomy	Nociceptive (somatic and visceral) and neuropathic	Mild to severe
Lower abdomen		
Hysterectomy	Nociceptive and neuropathic	Mild to severe
Radical prostatectomy	Nociceptive	Moderate to severe
Hernia	Nociceptive and neuropathic	Mild to severe
Extremities		
Vascular surgery	Nociceptive	Mild to moderate
Hip replacement	Nociceptive	Mild to severe
Knee replacement	Nociceptive	Moderate to severe
Arthroscopy, arthroscopic surgery	Nociceptive	Mild to moderate
Amputation	Nociceptive and neuropathic	Moderate to severe
Shoulder joint surgery	Nociceptive	Moderate to severe
Spine		
Laminectomy, discectomy	Nociceptive and neuropathic	Mild to severe
Spinal fusion	Nociceptive and neuropathic	Moderate to severe

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6

Postoperative analgesia

6.1 Non-pharmacological methods

Psychological methods

In the literature on postoperative pain management, the use of special psychological methods (distraction, biofeedback) is mentioned primarily in preoperative preparation, with ambiguous results. When used as an adjuvant therapy, they reduce patient anxiety and improve satisfaction with treatment. In several studies mainly on abdominal hysterectomy, these methods led to a reduced consumption of analgesics postoperatively, or to a lower pain score on the second or third postoperative day. Psychological methods are of potential benefit in patients with a high need for self-control and motivation for using them, such as reluctance to take drugs. The advantages of these methods are that they have virtually no contraindications, unless instrumental equipment is required (e.g. for biofeedback), they are easy to learn and can be performed by the patient at home. However, they are not suitable for patients who are not willing or able to cooperate. Most guidelines do not include them as a standard part of treatment.

Hypnosis
Hypnosis is a transient state of altered attention, in which various phenomena may occur spontaneously or in response to verbal and other stimuli. These phenomena include changes in consciousness and memory, and higher susceptibility to suggestions, reactions, and thoughts. Historically, hypnosis achieved greatest popularity through the work of F. A. Mesmer (1734–1815; animal magnetism, mesmerism) and was even used to relieve pain during surgery before the discovery of general anesthesia (1846). Thanks to its proven efficacy, general anesthesia replaced hypnosis in operating rooms soon after its successful demonstration. Nowadays, if hypnosis is used in perioperative care at all, it is primarily used for procedures performed under local anesthesia, where it induces a non-pharmacological sedation and reduces anxiety. Reports on its use in postoperative analgesia are scarce and for lack of evidence of its efficacy in relieving acute pain, hypnosis is not recommended in postoperative pain management.

Physical methods

Cold
Cold increases the threshold of pain, reduces local swelling and muscle spasm. It is used for a limited period of time after tooth extraction, small surgical procedures on the knee, minor incisions, etc. Long-term application is unpleasant and may cause trauma. Thus, the significance of cold in standard postoperative pain management is limited.

Heat
Heat relaxes muscle spasms and improves joint mobility. It is not used in the treatment of acute postoperative pain, as it increases the risk of bleeding and edema formation. Heat can be applied no sooner than 48 hours after surgery to enhance rehabilitation and local blood supply.

Immobilization
Although immobilization reduces pain, prolonged immobilization is not desirable due to an increased risk of deep venous thrombosis, pressure sores, muscle wasting, and complex regional pain syndrome. The aim of postoperative pain management is also to effectively relieve pain during movement.

Massage
Massage belongs to manual stimulation techniques and as an adjuvant method it is irreplaceable in the general treatment of pain. Massage mechanically improves blood supply, lymphatic drainage, reduces sensitization of tissues, and has an overall positive psychological effect. Contraindications include fresh skin lesions covered with grafts, hematomas, infection, malignancy, pleural effusion, liver and kidney disease, congestive heart failure, carotid artery disease, and deep venous thrombosis. In acute postoperative pain management, massage belongs to adjuvant techniques that are either omitted, or not evaluated in most standard recommendations.

Acupuncture
Acupuncture belongs to stimulation techniques, which are irreplaceable in the therapy of both acute and chronic pain. However, it is only rarely mentioned in connection with postoperative pain management. In the perioperative period, acupuncture has proved to reduce the incidence of postoperative nausea and vomiting, yet reports of its effectiveness in alleviating postoperative pain are controversial. In theory, acupuncture has only a few adverse effects, however, serious complications caused by infection, broken and "wandering" acupuncture needles, and an incorrect insertion of the needle have been reported. Another problem when evaluating its efficacy is that acupuncture covers a variety of specific techniques. Most official guidelines do not mention the use of acupuncture in postoperative analgesia or do not recommend it for lack of evidence of its efficacy.

Transcutaneous electrical nerve stimulation (TENS)
TENS is a method based on the gate control theory of pain. Using skin electrodes, nerve fibers are stimulated by a defined electrical current. In addition, the use of TENS also has a significant placebo effect. Carrol did not report any significant analgesic effect of TENS in 352 women during childbirth, yet most of them would prefer having TENS

again. In postoperative pain management, TENS has been used as an adjuvant method, which may lead to a reduced consumption of analgesics after surgery, enhanced rehabilitation, improved lung function, blood perfusion in both the stimulated and distant dermatomes, and increased patient satisfaction with the treatment. TENS is effective mainly in treating mild pain (e.g. after inguinal hernia repair and laparoscopic cholecystectomy, but not after open cholecystectomy). Disadvantages include the need to purchase the device, use of electrodes and patient education.

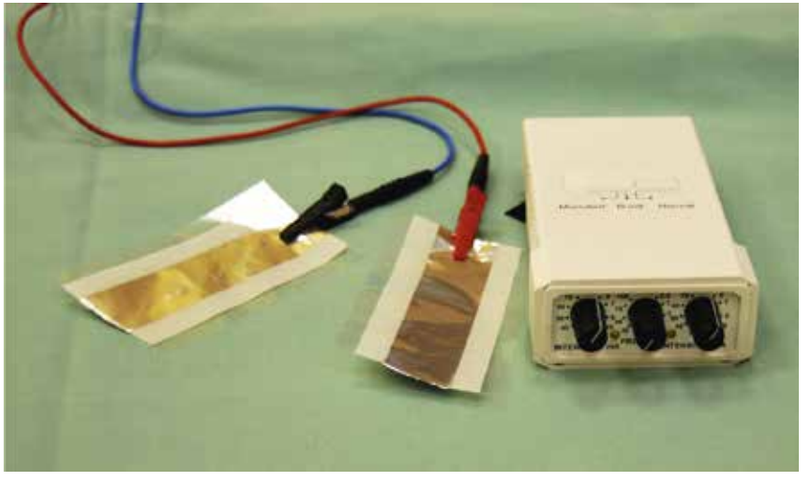

Fig. 6.1 TENS device

An artificial cardiac pacemaker is a contraindication, despite several authors allowing its use in this situation. TENS is devised primarily for chronic pain treatment; standard guidelines do not recommend it in acute postoperative pain management, since a positive benefit-cost ratio has not been proved (Fig. 6.1).

Rehabilitation
Rehabilitation improves postoperative course, shortens recovery time and hospital stay and prevents complex regional pain syndrome. On the other hand, rehabilitation may cause procedural pain, therefore it is advisable to administer a dose of analgesic beforehand.

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6.2 Systemic pharmacotherapy

6.2.1 Routes of administration

Oral administration
Oral administration is the most commonly used route of administration in medicine. Its main advantages are non-invasiveness, ease of use and self-administration. Many analgesics are only available in oral form. In postoperative analgesia, its main drawback is that the patient must be able to swallow and absorb the medication. This can be a problem in certain postoperative conditions or their frequent complications, such as nausea and vomiting. Another problem may be the slow onset of action and more difficult dose titration, which in practice may lead to underdosing rather than overdosing of analgesics. Nevertheless, oral administration of analgesics after surgery is recommended, unless there is a contraindication.

Rectal administration
The advantage of absorption from rectal mucosa is that it largely bypasses the first-pass hepatic metabolism of the drug. Disadvantages are similar to oral administration. Besides, this route of administration is not accepted very well by the patients.

Intramuscular, subcutaneous administration
Intramuscular injection is the most common route of administration for analgesics in the postoperative period. In most patients, it is possible to achieve satisfactory analgesia, despite major differences in absorption from the site of administration and despite the fact that the administration may be unpleasant and painful. It is important to remember that this route of administration is contraindicated in postoperative blood coagulation disorders.

An advantage is that it can be used in patients who are incapable of oral intake and that patient cooperation is not essential. Furthermore, parenteral route of administration has a strong placebo effect.

Cases of damage to neural structures and more frequent hematoma formation following an intramuscular injection have been reported, therefore subcutaneous injection or intravenous administration is preferable, if possible (e.g. in opioid administration). Intramuscular administration of opioids is considered obsolete. A permanent thin needle or cannula may be left in the subcutaneous tissue for repeated administrations, which prevents repeated punctures. This way even small volumes may be administered continuously.

Intravenous administration
Compared to the previously mentioned methods, intravenous administration has the advantage of a faster onset of action, efficacy at lower doses and easier dose titration. On the downside, venous access must be secured, a higher risk of wrong dose has been reported in literature and there is a greater risk of side effects.

Patient-controlled analgesia (PCA)
PCA is a method, which allows the patients to administer the analgesic (opioid) themselves, most commonly in the vein or epidural space, although other routes of administration have been reported as well (subcutaneous, transdermal iontophoretic, etc.). Basic parameters, which are set by the physician in advance and cannot be changed by the patient, include bolus dose administered when the patient pushes the button, lock-out interval – time during which the machine will not administer a further dose despite any further demands made by the patient, and usually the maximum dose to be given per 4 or 6 hours. The patient should be given a loading dose of analgesics to effectively relieve pain before starting PCA. PCA requires patient cooperation (it may be used in children over 6 years of age) and physical ability to operate the device. Compared to other types of systemic opioid administration, the main advantages of PCA are greater patient satisfaction and better-quality analgesia. Side effects are identical to other routes of administration. Besides bolus administration, the device usually allows background infusion of the analgesic, which according to several studies may increase the risk of overdose and has no influence on the quality of analgesia (Fig. 6.2).

Fig. 6.2 PCA device

Table 6.1 Systemic opioid doses for patient-controlled analgesia

Medication	PCA bolus	Lock-out interval (min.)
Morphine	0.5–2.5 mg	5–10
Fentanyl	50–100 mcg	3–10
Sufentanil	2.5–5 mcg	3–10

For non-invasive administration, a PCA device using sufentanil sublingual tablets and fentanyl nasal spray, or iontophoretic administration of fentanyl through intact skin is registered.

Non-traditional routes of systemic administration
Non-traditional routes of administration include transmucosal, conjunctival and inhalational administration of opioids. With the exceptions mentioned in the previous paragraph, these methods are still in research and development stages.

Regional administration of analgesics
The advantage of regional administration of analgesics is that it largely eliminates their systemic effects (depending on the absorption into the circulation). The techniques range from wound infiltration before closure to various blockades of the individual nerves (intercostal nerve blockade, lower limb nerve blockades, paravertebral blockade), neural plexuses (brachial and cervical plexus blockades), and central nerve blockades (epidural and spinal). In general, regional administration provides better analgesia than systemic administration. The duration of action depends on whether it is a single-injection or catheter technique. A disadvantage is that they are more technically challenging and often more invasive with all the associated risks. The various techniques are described in more detail in section 6.3.

6.2.2 Drugs

Neither this section, nor any other sections on the dose and use of drugs are a substitute for detailed information contained in pharmacology textbooks and SPCs (Summary of Product Characteristics) of each drug. It is essential that anyone prescribing medication be previously acquainted with up-to-date information on its dose, indications, contraindications and adverse effects, as well as with the latest standards of the methods used.

Non-opioid analgesics

Paracetamol (acetaminophen)

Paracetamol is an analgesic and antipyretic agent that lacks anti-inflammatory properties, with good gastrointestinal tolerability, suitable for both pediatric and adult patients. It has minimal side effects. One of its advantages is that it does not significantly affect blood clotting, not even in patients receiving oral anticoagulants (it may be used in hemophiliacs), and it does not affect blood glucose levels. In postoperative analgesia, paracetamol is used for mild to moderate pain and in combination with other medications (opioids in particular) to treat severe pain. According to the Oxford

League table of analgesic efficacy (Bandolier, see 6.4 Multimodal analgesia), the combination of paracetamol and tramadol or codeine is more effective than pethidine or morphine in clinical doses. It should be noted, however, that although the comparison is based on high-quality randomized trials, these trials were conducted mainly in patients with mild pain (see section 6.4). Paracetamol does not affect uric acid levels and its excretion in the urine. The mechanism by which paracetamol produces analgesia is not yet fully understood. It is available in a variety of forms (oral, rectal, intravenous), and especially the intravenous form is designed for postoperative analgesia. Intravenous administration has the advantage of a rapid onset of action. If IV paracetamol is administered before the end of surgery, analgesia is already effective after recovery from anesthesia. By contrast, absorption after rectal administration is uncertain, as the first dose may not achieve an effective concentration even at 40 mg/kg.

Dosage

Oral or rectal administration

Adults and adolescents receive 0.5–1 g of paracetamol as needed in intervals of at least 4 hours, to a maximum dose per day of 4 g, the maximum single dose is 1 g. In long-term treatment (over 10 days), the dose per day should not exceed 2.5 g. Paracetamol can be administered during pregnancy and lactation.

In children, the total dose per day should not exceed 50 mg/kg of body weight; it is divided into 3–4 individual doses. The dose for single administration is 10–15 mg/kg of body weight.

Note:

Kršiak et al. have demonstrated that the usual adult dose of 1–2 tablets orally leads to underdosing in overweight patients and the dose should be increased up to 3 tablets, knowing that it is more than the dose recommended in the SPC.

Intravenous administration

The paracetamol solution is administered as a 15-minute intravenous infusion. The minimum interval between each administration must be at least 4 hours. In adults and adolescents weighing more than 50 kg, 1 g of paracetamol is administered up to four times a day, the maximum dose per day is 4 g. In children weighing more than 33 kg (approx. from 11 years of age) or in adults and adolescents weighing less than 50 kg, the single dose is 15 mg/kg, the maximum dose per day is 60 mg/kg (not exceeding 3 g). In children weighing more than 10 kg (approx. from 1 year of age) and less than 33 kg, the single dose is 15 mg/kg, the maximum dose per day is 60 mg/kg (not exceeding 2 g). In term newborn infants, infants, toddlers and children weighing less than 10 kg (approx. until 1 year of age), the single dose is 7.5 mg/kg of body weight, the maximum dose per day must not exceed 30 mg/kg of body weight.

Toxicity

Overdose by relatively low doses of paracetamol can cause serious liver damage and may sometimes result in acute renal tubular necrosis. Nausea, vomiting, lethargy, and sweating may occur within 24 hours. Abdominal pain, which occurs in 1–2 days, may be the first sign of liver damage. Liver failure, encephalopathy, coma, and death may develop. Complications of liver failure include acidosis, cerebral edema, bleeding, hypoglycemia, hypotension, infection, and renal failure. Prolongation of prothrombin time indicates deteriorating liver functions, therefore monitoring prothrombin time is recommended. Patients who receive enzyme inducers (carbamazepine, phenytoin, barbiturates, rifampicin) or have a history of alcohol abuse, are more prone to liver damage. Acute renal failure can occur even in the absence of severe liver damage. Other symptoms of intoxication include myocardial damage and pancreatitis.

Treatment of overdose: Hospitalization is required. It is necessary to induce vomiting and perform gastric lavage, particularly if paracetamol was ingested less than 2 hours ago. Methionine should be administered (2.5 g orally) and supportive measures are recommended. The administration of activated charcoal to reduce gastrointestinal absorption is questionable. Monitoring plasma concentrations of paracetamol is recommended. Acetylcysteine, a specific antidote, should be administered within 8–15 hours after intoxication, however, beneficial effects were observed even when given after this time. Acetylcysteine is usually administered to adults and children intravenously in 5% glucose, with an initial dose of 150 mg/kg of body weight over 15 minutes, followed by 50 mg/kg in a 5% glucose infusion over 4 hours, and then 100 mg/kg until 16, or 20 hours after starting the therapy, respectively. Acetylcysteine may also be administered orally within 10 hours after the ingestion of a toxic dose of paracetamol, at a dose of 70–140 mg/kg three times a day. In very severe intoxications, hemodialysis or hemoperfusion is possible.

Note:

The concurrent administration of paracetamol and 5-HT3 antagonists (with the exception of ondansetron) leads to reduced effectiveness of both medications. In case of long-term administration, it is necessary to take into account other interactions and risks (potentiation of the effect of coumarin derivatives, increased risk of hypertension and myocardial ischemia, etc.). However, in common postoperative pain management these are not of much concern.

Metamizole

Metamizole is an analgesic and antipyretic agent with spasmolytic properties. Although it is also available in oral form, in postoperative analgesia it is primarily used in infusion. In children aged 3 to 11 months, only intramuscular injections can be used. Metamizole must not be used during the third trimester of pregnancy and during lactation (lactation is to be avoided during administration and for 48 hours after the administration of metamizole). Besides allergy, contraindications include hematopoietic disorders, allergic asthma induced by nonsteroidal anti-inflammatory drugs, hepatic porphyria, and glucose-6-phosphate dehydrogenase deficiency. Caution is advised in patients with other forms of asthma, chronic urticaria, alcohol intolerance, in the elderly, and in case of hypotension and hypovolemia.

Adverse effects

The most feared, albeit rare adverse effect is a severe, life-threatening anaphylactic/anaphylactoid reaction, more often in the form of a skin reaction. Allergic reaction may develop even several hours after the administration. Furthermore, isolated hypotension may occur. Rare cases of leukopenia have been noted. Agranulocytosis or thrombocytopenia and renal failure are very rare.

Dosage

Adults: the single dose is 8–16 mg/kg of body weight for oral administration, 6–16 mg/kg of body weight for parenteral administration, the maximum dose per day is 5 g, in

children usually 10–15 mg/kg, up to four times a day. In children aged 3-11 months, only intramuscular injection may be used. Rapid infusion administration causes hypotension, which is more pronounced if hypovolemia is present. The dose of 2.5 should be given in a 500-mL infusion.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Most of the presumed effect of NSAIDs is caused by the inhibition of cyclooxygenase (COX), which catalyzes the formation of prostaglandins from arachidonic acid. NSAIDs have both a peripheral effect (at the injury site) and effect at the level of the spinal cord where prostaglandins are supposed to interfere with descendent anti-nociceptive pathways. NSAIDs inhibit this interference and allow better central pain control. Peripheral analgesics have a **ceiling effect**, and increasing the drug dose does not increase its effectiveness, therefore they are used in combination with opioids to treat severe pain. In this combination, NSAIDs may reduce the total dose of opioids by up to 46%.

Cyclooxygenase is present in the human body in two forms: COX-1 and COX-2. While COX-1 is considered a constitutive enzyme responsible for the synthesis of prostaglandins, which play an important role in the homeostasis of the human body (gastrointestinal mucosal blood flow, gastric mucosa protection, renal perfusion, platelet aggregation, protection of the endothelium), COX-2 is mainly induced during inflammation and participates in the production of proinflammatory cytokines and pain mediators. It was assumed that novel compounds selectively inhibiting COX-2 would be safer and have fewer side effects. Indeed, it was confirmed that selective COX-2 inhibitors are safe in terms of the risk of increased gastrointestinal bleeding and disorders of platelet function. On the other hand, adverse effects on renal function turned out to be identical to those of nonselective COX inhibitors, and selective COX-2 inhibitors also have a potentially adverse effect on the cardiovascular system, which is dependent on the dose and duration of the administration. A recent meta-analysis has demonstrated that adverse effects on the circulatory system are not limited to selective COX-2 inhibitors, as with prolonged use all NSAIDs exhibit these effects (when compared to placebo, rofecoxib showed the highest risk of myocardial infarction – odds ratio (OR) 2.12, ibuprofen has the greatest risk of stroke – OR 3.36, followed by diclofenac – OR 2.86, and a prolonged use of etoricoxib, or diclofenac is associated with the highest risk of cardiovascular death – OR 4.07, or 3.98, respectively). Whether these findings have any clinical relevance for short-term administration in postoperative pain management is of course questionable. The strict differentiation of the two isoenzymes as COX-1 – beneficial and COX-2 – harmful has been recently challenged and it seems that the situation is much more complex than originally thought. Nevertheless, based on the assumed effect on platelet function, NSAIDs can be divided into 3 groups, in which the risk of bleeding complications decreases with increasing selectivity of COX-2 inhibition, which is particularly important in the immediate perioperative period. Due to their adverse effects, NSAIDs are generally not recommended in patients over 65 years of age. This applies in particular to long-term administration (more than 3 weeks). In acute postoperative pain management, short-term administration of NSAIDs (up to 1 week) is possible, or NSAIDs can be used in combination with proton pump inhibitors.

The effects of NSAIDs on the healing of bones, soft tissues, and intestinal anastomoses have also been studied. While the first two effects have not been confirmed, there is evidence that NSAIDs should not be administered in acute colorectal surgery with intestinal anastomosis due to the risk of wound dehiscence. In scheduled colorectal procedures with anastomoses, this risk is low to negligible.

Nonselective COX inhibitors

Currently, the most widely used NSAIDs are derivatives of arylalkanoic acids – acetic acid (e.g. diclofenac, indometacin) and propionic acid (e.g. ibuprofen, naproxen). Another group of NSAIDs are oxicams (e.g. piroxicam), which have a long biological half-life in comparison to arylalkanoic acids derivatives, and are generally administered in a single dose per day. Fenamates also have very good analgesic and anti-inflammatory effects.

Diclofenac

Diclofenac has excellent analgesic properties and is particularly effective for pain with an inflammatory component and pain after tooth extraction. Adverse effects are typical for the whole group. Diclofenac is contraindicated in pregnancy and during lactation. It is available in oral and injectable form for IM administration or infusion in adults only.

Oral administration: the initial dose in adults is 100–150 mg per day; 75-100 mg is usually sufficient in less severe conditions and in children over the age of 12. The total dose per day is divided into 2–3 single doses and should not exceed 150 mg/24h in adults. Children weighing more than 20 kg (the only indication is juvenile chronic arthritis) are administered 1–3 mg/kg of body weight per day, divided into 2–3 doses.

Adults – intramuscular (IM) injection: deep intramuscular administration of 75 mg of diclofenac into the upper outer quadrant of the gluteal muscle, 150 mg in case of severe pain.

Adults – intravenous (IV) infusion: diclofenac must not be given as an IV bolus. Infusion with 75 mg of diclofenac must be administered over 0.5–2 hours and must be prepared immediately before administration. In order to prevent postoperative pain, 25–50 mg of diclofenac in a 15-minute to 1-hour infusion is administered immediately after the procedure, followed by a continuous infusion of 5 mg/h, up to the maximum dose per day. The total dose per day should not exceed 150 mg of diclofenac. Infusions should not be administered for more than two days.

Note:

The combination of diclofenac with a centrally acting muscle relaxant called orphenadrine should produce, in addition to the analgesic and anti-inflammatory effects, a spasmolytic effect on skeletal muscles. This is beneficial after orthopedic surgical procedures, or any procedure with a predominantly somatic pain, as it suppresses reflex muscle spasm, which would otherwise exacerbate the pain. This combination (the commercially available product Neodolpasse contains 75 mg of diclofenac and 30 mg of orphenadrine in a 250-mL infusion) may be given to patients over 14 years of age. Besides the side effects and contraindications of diclofenac, which were already mentioned at the beginning of the chapter, the combination with orphenadrine also has parasympatholytic effects and is contraindicated in paralytic ileus, myasthenia gravis, and similar conditions. The infusion should be given over 1.5-2 hours. One, or a maximum of two infusions per day are administered at intervals of at least 8 hours.

Ibuprofen
Ibuprofen is used to treat pain in patients over 3 months of age (weight > 6 kg). Its side effects are typical for the whole group of NSAIDs, but are considered mild. Ibuprofen is contraindicated in the third trimester of pregnancy and is not recommended in the first and second trimesters either. However, it can be used during lactation. In the United States, ibuprofen is also registered in injectable form, marketed under the name Caldolor.

The total dose per day for adults should not exceed 2,400 mg, divided into 3–6 doses.

The total dose per day for children under the age of 12 is 20–35 mg/kg of body weight, divided into 3–4 doses.

Ketorolac
Ketorolac is a nonsteroidal anti-inflammatory drug used for short-term treatment of pain (up to 5 days) in adults and children over 2 years of age. It is available in oral and parenteral form (IM or IV administration). It is recommended to always start with parenteral formulation (30 mg IV, or 60 mg IM, to a maximum dose per day of 120 mg) and gradually switch to oral formulation with an initial dose of 20 mg, followed by 10 mg doses four times a day. The maximum dose per day for oral administration is 40 mg. Increasing the dose does not produce better effect. Lower doses are recommended in the elderly and in patients with renal insufficiency. Adverse effects are identical to those of other drugs in this group.

Ketoprofen
Ketoprofen is a nonsteroidal anti-inflammatory drug used to treat pain in patients over the age of 15. When administered orally, ketoprofen has high bioavailability (up to 90% in comparison with IV administration). Parenteral treatment should not last for more than 48 hours, the dose is 200 mg once or twice a day injected deep into the muscle or given in an infusion over 30 to 60 minutes. Contraindications include severe kidney or liver disease; other contraindications and adverse effects are common with other NSAIDs.

Naproxen
Naproxen is only available in oral form for the treatment of acute pain in patients over the age of 12. The dose of 550 mg up to three times a day effectively treats mild to moderate postoperative pain. In combination with a weak opioid, it may be used to treat severe pain. Naproxen is not suitable in pregnancy, but may be used during lactation. Adverse effects are identical to those of other drugs in this group.

Piroxicam
Piroxicam is available in injectable (only IM) and oral form. In comparison to other drugs in this group, it seems to have higher risks (adverse effects on the gastrointestinal tract and a higher risk of skin reactions, including life-threatening bullous reaction). The advantage is once a day dosing. Piroxicam can be used to treat acute postoperative pain in patients over the age of 14. Contraindications include pregnancy and lactation. A dose of 40 mg of piroxicam is administered once a day to treat severe pain, 20 mg to treat mild pain. The duration of the treatment should be individualized, usually 1 or 2 days are recommended. In 2011, a warning was issued that piroxicam may in rare cases cause Stevens-Johnson syndrome and toxic epidermal necrolysis.

Preferential COX-2 inhibitors

Meloxicam
Meloxicam is available in injectable (only IM) and oral form. The approved indications do not include acute postoperative pain; however, especially the oral form is sometimes used in adults. Adverse effects are common with other NSAIDs, contraindications include pregnancy and lactation. The advantage of meloxicam is its long duration of action. The dose is 15 mg once a day. In 2011, a warning was issued that meloxicam may in rare cases cause Stevens-Johnson syndrome and toxic epidermal necrolysis.

Nimesulide
Nimesulide is registered for the treatment of acute pain in patients over the age of 12. Due to the risk of hepatotoxicity, treatment should be restricted to a minimum. Contraindications include impaired liver function and severe renal insufficiency. Nimesulide is used as a second-line therapy for chronic pain. It is only available in oral form; the dose is 100 mg twice a day.

Selective COX-2 inhibitors – coxibs

Parecoxib
Parecoxib is the only medication in this group, which is specifically designed for short-term postoperative pain management in patients over the age of 18. Adverse effects and contraindications – see the general characteristics of NSAIDs. Parecoxib is contraindicated for the treatment of pain after coronary artery bypass surgery, in the third trimester of pregnancy, and during lactation. Other restrictions are similar to those of other NSAIDs. Its availability in injectable form is beneficial in the perioperative period, even if there are concerns about impaired platelet function (spinal block, ENT procedures, endoscopic urological procedures). Parecoxib is administered IV or IM in a dose of 40 mg, the maximum dose per day is 80 mg.

Celecoxib
Celecoxib is not registered for the treatment of postoperative pain, yet it is sometimes used due to its reduced effect on bleeding (e.g. after ENT procedures and endoscopic urological procedures). It is contraindicated in pregnancy and during lactation. Celecoxib is only available in oral form, the dose for adults is 200 mg per day, in 1–2 doses.

Etoricoxib
This selective COX-2 inhibitor is registered for the treatment of osteoarthritis, rheumatoid arthritis, pain and signs of inflammation associated with acute gouty arthritis in patients over the age of 16. Less than 20 articles have been published on etoricoxib in the treatment of acute postoperative pain. It has been mainly used preoperatively in a single dose of 120 mg, which led to a decreased opioid requirement, thereby reducing their adverse effects.

Opioid analgesics

Opioid analgesics act on opioid receptors present in the central nervous system and elsewhere. Analgesic effects are mainly attributed to μ-opioid receptors (supraspinal analgesia, euphoria and drug dependence, miosis, respiratory depression, bradycardia,

and reduced bowel motility) and κ-opioid receptors (spinal analgesia, miosis and sedation). Based on their affinity (receptor binding strength) and intrinsic activity (efficacy – producing the typical effect after binding to the receptor), opioid analgesics can be divided into several groups:

- opioid agonists – display high affinity, as well as high intrinsic activity, induce the typical effects of opioids (morphine, pethidine, piritramide, fentanyl and its other derivatives)
- opioid antagonists – display strong affinity, but zero intrinsic activity, used as an antidote (naloxone)
- κ-opioid agonists – antagonists at μ-receptors (butorphanol, nalbuphine)
- partial μ-agonists – display high binding affinity, but lower intrinsic activity (buprenorphine)

In postoperative pain management, μ-opioid agonists are used almost exclusively (with the exception of nalbuphine). In general, more potent opioid analgesics show a more favorable ratio between the effective dose and the dose, at which adverse effects occur. Weak opioids have a ceiling effect, i.e. increasing the drug dose does not increase its effectiveness. Strong opioids do not show this effect; however, the maximum dose is limited by their adverse effects (respiratory depression). Opioid analgesics are generally not able to completely relieve severe pain, but by affecting mood, they suppress the discomfort associated with pain. Because of these effects on mood, opioids may be abused for recreational purposes with all the related adverse effects. Therefore, special regulations apply to most opioid analgesics.

Adverse effects of opioid analgesics include respiratory depression (at higher doses), nausea and vomiting, decreased intestinal motility and gastric emptying, increased sphincter tone, sphincter of Oddi spasm with bile stasis, decreased secretion of pancreatic juice and bile, urinary retention, sedation, in rare cases euphoria or dysphoria. **The most feared complication – respiratory depression – first manifests as a decrease in the respiratory rate**, a decline in SpO2 will only develop later, especially if the patient receives oxygen after surgery. Sedation and disorders of consciousness are late symptoms. When administering opioid analgesics, an antidote (naloxone) must always be available (see below). A lesser-known adverse effect is muscle rigidity. When administering opioid analgesics (intraspinally in particular), itching may appear. Opioids may cause a drop in the blood pressure and bradycardia due to vagal nerve stimulation. Furthermore, the cardiovascular response to stress is inhibited, which may result in orthostatic collapse in some patients. Opioid therapy in children is described in Chapter 8.

After a prolonged administration of opioid analgesics, tolerance both to certain adverse effects (sedation, nausea) and to the analgesic effect develops, and the dose needs to be increased. Psychological dependence develops in connection with the indicated use in pain therapy only rarely. Physical dependence always develops, usually after 20–25 days, sometimes even sooner, and withdrawal symptoms occur after rapid discontinuation of opioid treatment. Recently, hyperalgesia has been linked to opioid analgesics – paradoxically, substances that alleviate pain may lower the threshold of pain (see below). Thus, a decreased efficacy of opioids may be caused not only by tolerance to their analgesic effects, but also by hyperalgesia. In this context, remifentanil is most commonly mentioned, and it should not be used in patients on long-term opioid therapy at all.

Contraindications of opioid analgesics include hypersensitivity, intracranial hypertension, craniocerebral injury without artificial ventilation, treatment with monoamine oxidase inhibitors, porphyria. Normal doses of opioid analgesics for short-term postoperative pain management are safe in pregnancy and during lactation. However, as they cross the placental barrier, caution should be exercised in the period immediately before delivery to prevent neonatal respiratory depression. Pediatric administration generally requires enhanced monitoring of respiratory functions, particularly after surgery. Higher sensitivity to opioid administration has been reported in the elderly (risk of deeper sedation, confusion, hallucinations), and in patients with reduced function of kidneys and thyroid gland.

Opioid-induced hyperalgesia

Although opioid-induced hyperalgesia (OIH) is mainly associated with the treatment of chronic pain, more recently it has been shown that it develops in the treatment of acute pain as well. OIH is based on the fact that substances that are supposed to inhibit pain perception decrease the threshold of pain or pain tolerance, presumably by central sensitization. At dorsal horn level, an ongoing stimulation from the periphery results in an increased number and altered response of the receptors involved in pain pathways, such as N-methyl-D-aspartate (NMDA) receptors. The result is hyperalgesia – a decreased pain threshold, or allodynia – pain triggered by stimuli, which do not normally provoke pain, even in an area which is not directly injured. Different terms are being used for this phenomenon: physiologists tend to use opioid-induced hyperalgesia, while pharmacologists describe it as acute tolerance to the analgesic effect of opioids. Both phenomena are likely to have the same underlying pathophysiology and identical clinical manifestations, yet several differences can be theoretically found: in acute tolerance, the pain threshold does not change, there are no symptoms of allodynia or secondary hyperalgesia, and an increased opioid dose will lead to greater pain relief, whereas in opioid-induced hyperalgesia, an increased dose of opioids will not result in pain relief (theoretically, discontinuation of opioid therapy should lead to an improvement). Experiments on animals have shown that repeated administration of different opioids using various routes of administration lowers the basic pain threshold and that this effect lasts for up to 5 days. Theoretical clinical implications could be observed in opioid-dependent persons (therapy, abuse) and in patients who receive opioid analgesics perioperatively. Indeed, it has been demonstrated that opioid withdrawal before surgery leads to impaired perception of pain after surgery; in some cases, perioperative administration of opioid analgesics (remifentanil in particular) increases postoperative pain and/or consumption of opioid analgesics. Several studies have reported a lower quality of postoperative analgesia in patients who received morphine before surgery for the treatment of chronic or cancer pain.

There are several possible solutions to the problem, many of which are routinely used, without it being due to the risk of acute tolerance or hyperalgesia. These include, for example, multimodal analgesic techniques, which reduce opioid consumption and may also reduce the risk of hyperalgesia. Another option is to use opioid analgesics with a unique profile (methadone, buprenorphine), NMDA receptor antagonists (ketamine, dextromethorphan), add a small amount of an antidote to opioid analgesics, or experimentally administer cannabinoids.

Much remains unknown: can we distinguish between hyperalgesia and tolerance? Can hyperalgesia be prevented or treated? Is there a difference among the various opioid analgesics in the development of hyperalgesia and, if so, why? Does the route of administration make a difference? How long does it take to develop OIH and at what doses?

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Weak opioid analgesics

Tramadol
Tramadol has several unique features. It acts by binding to opioid receptors, but also by inhibiting the reuptake of serotonin and noradrenalin. Tramadol is metabolized to O-desmethyltramadol, which is a more potent opioid. It is available in many forms for parenteral, oral, and rectal administration. Tramadol alone is only effective for mild pain, but in combination with NSAIDs or non-opioid analgesics it has more potent analgesic effects. On the downside, nausea, vomiting and dizziness frequently develop. Tramadol may increase the effect of selective serotonin reuptake inhibitors – SSRIs (risk of life-threatening serotonin syndrome), tricyclic antidepressants, antipsychotics, and other drugs that lower the seizure threshold, and may provoke seizures as well. Tramadol should not be administered together with monoamine oxidase inhibitors. A concurrent administration of a 5-HT3 receptor antagonist (such as ondansetron) reduces the effect of tramadol. Recently, FDA issued warning that tramadol should not be used to treat pain in all children younger than 12 years and in children younger than 18 years after the removal of tonsils and/or adenoids. No such warning was given by the European Medicines Agency and other authorities.

Dosage
Patients over 1 year of age are given 1–2 mg/kg every 4–6 hours, the dose per day in adolescents and adults should not exceed 400 mg.

Codeine
After administration, codeine is partially metabolized to morphine. About 10 to 15% of patients do not metabolize codeine in this way due to different genetic makeup and are therefore "resistant" to its analgesic effect. On the other hand, there is a group of ultrarapid metabolizers with an increased risk of overdose. A fatal respiratory depression has been reported in a newborn, whose mother took analgesics containing codeine during lactation and belonged to this rare group. Similar complications have been observed in pediatric patients after ENT surgery. **A number of international authorities contraindicate the use of codeine in all children under the age of 12 and in children under the age of 18 after adenoidectomy and/or tonsillectomy.** The dose in adults is 1 mg/kg.

Dihydrocodeine
Dihydrocodeine has similar properties to codeine and is registered for the treatment of moderate to severe pain. It is not considered suitable for the basic treatment of acute postoperative pain.

Strong opioid analgesics

Morphine
Morphine is a prototypical strong opioid, which remains the gold standard against which all drugs that have strong analgesic effects are compared. Everything that has been stated in the section on general characteristics of opioid analgesics applies to morphine as well. Various routes of administration are available (oral, intramuscular, subcutaneous, intravenous, epidural, spinal, intra-articular). In postoperative pain management, parenteral administration is preferred. Morphine is metabolized to morphine-6-glucuronide, an active metabolite, which is excreted by the kidneys. Therefore, renal insufficiency may lead to morphine accumulation and prolonged effect. For systemic analgesia, the dose is 0.1 mg/kg, the duration of action is about 4 hours.
Piritramide
Piritramide exhibits similar effects to morphine, but has a longer duration of action (about 6 hours). Its elimination is not dependent on renal function.

Dosage
For intramuscular or subcutaneous administration, the recommended single dose is 15–30 mg in adults and 0.05–0.2 mg/kg of body weight in children. For intravenous administration (only when a particularly rapid onset of action is required), the recommended dose in adults is 7.5–22.5 mg administered slowly (10 mg per minute). A single dose for children is 0.05–0.1 mg/kg of body weight. If the effect is not sufficient, intramuscular, subcutaneous or intravenous administration may be repeated every 6–8 hours. The dose should be reduced in the elderly and in patients with impaired liver function or in poor physical condition.

Pethidine (meperidine)
In addition to its opioid effect, pethidine also has the characteristics of a weak local anesthetic and alpha-2 agonist. Pethidine has many side effects, for which it is not suitable in postoperative pain management. Its effect is short-term at first, but it gradually accumulates in the body. Pethidine is metabolized to norpethidine, which is neurotoxic and can provoke seizures. Intramuscular, subcutaneous and intravenous routes of administration are available. Pethidine should not be used during lactation for an extended period of time, as it may cause neurobehavioral changes in infants. The dose is approx. 1 mg/kg every 4 hours, to a maximum dose per day of 300 mg in adults.

Fentanyl, sufentanil, alfentanil, remifentanil
In systemic analgesia, short-acting opioids are administered by titration or continuously with the possibility of adding a bolus, mostly IV, until the desired effect is achieved. Their use is limited to operating rooms, recovery rooms and intensive care units. Non-traditional ways of fentanyl administration, which were previously used for postoperative analgesia, are currently unavailable. Iontophoretic transdermal fentanyl administered by patient-controlled analgesia was withdrawn from the mar-

ket for several years, but is now available again in Europe. Transmucosal fentanyl (inhaled nasal spray, sublingual and buccal tablets), which combine non-invasive administration and rapid onset of action, are available. However, they are only intended for breakthrough pain in cancer patients, and their use in postoperative analgesia is contraindicated by the manufacturer.

Oxycodone
In many countries, oxycodone is the most commonly used opioid analgesic for the treatment of severe postoperative pain in adults. This is due to its favorable pharmacodynamics, high bioavailability after oral administration, which allows an easy transition from parenteral to oral form, and the fact that oxycodone can also be administered to adolescents, as well as to the elderly. Intravenous, intramuscular, nasal, mucosal, subcutaneous and oral (rapid-onset medication or tablets and capsules with controlled release) routes of administration have been reported in the literature. Oxycodone is metabolized in the liver, and both its metabolites and about 10 % of unchanged oxycodone are excreted by the kidneys. In orthopedic procedures and surgical procedures not involving visceral pain, intravenous oxycodone is equipotent to morphine, while in visceral procedures, it is more potent. Oxycodone is administered either by titration dose 0.05–0.1 mg/kg every 10–15 minutes (3 mg in adults, 1–2 mg in the elderly), or as a very slow bolus of 5–10 mg IV. The effect lasts for 4 hours. Another option is to use an infusion with an initial rate of 2 mg/h, or PCA (0.03 mg/kg bolus with a minimum lockout interval of 5 minutes). In subcutaneous administration, the dose is 5–10 mg every 4 hours. When using rapid-onset tablets, the dose in adults is 5–10 mg PO, the same applies to transmucosal administration (experimental). The adverse effects are identical to those of other strong opioid analgesics. Oxycodone should not be administered during delivery and lactation.

Hydromorphone
Although hydromorphone used to be very popular in the treatment of acute and chronic pain at the time of its introduction into clinical practice, nowadays it is rarely used for acute postoperative pain management and it is replaced with other medications. One of the reasons for its declining popularity is the fact that in many countries hydromorphone is only available in oral form with controlled release. Hydromorphone is five times more potent than morphine when given orally, and 8.5 times as potent when administered intravenously. It can be used in children and as a PCA. Adverse effects are similar to those of morphine, with lower incidence of itching.

Other opioid analgesics

Nalbuphine
Nalbuphine is a mixed κ-receptor agonist and μ-receptor antagonist. While it also causes respiratory depression comparable to 10 mg of morphine, increasing the drug dose does not intensify respiratory depression (ceiling effect). Respiratory depression is treatable with naloxone. Since nalbuphine antagonizes the effect of strong morphine-like opioids, it cannot be combined with them. The most common side effect is sedation. Nalbuphine should not be used in pregnancy and during childbirth (risk of life-threatening complications, such as fetal bradycardia, respiratory depression or arrest during childbirth, hypotension), however, some physicians use it for analgesia in labor and delivery, mostly in the form of an infusion. Nalbuphine passes into breast milk, thus breastfeeding should be discontinued for 24 hours after its administration. The dose for adults is 10–20 mg (0.1–0.3 mg/kg) IV, IM or SC every 3–6 hours. In children over 1.5 years of age, the dose is 0.1–0.2 mg/kg. Intramuscular and subcutaneous administration might be painful.

Tapentadol
Tapentadol is a newer analgesic acting as an agonist at the μ-opioid receptor and as a norepinephrine reuptake inhibitor. It is manufactured both in rapid-onset formulation for the treatment of acute pain, including postoperative pain, and in a sustained-release formulation (SR) for the treatment of chronic pain, in both cases only for oral use. Tapentadol was first marketed in the US and since January 2011, it is also registered in Europe. For the treatment of acute pain, it is available in tablets containing 50, 75, and 100 mg of tapentadol. There are not many studies on its use in postoperative analgesia, as most papers examine the use of tapentadol in the treatment of chronic pain. Tapentadol has been compared to oxycodone, but further studies comparing it to other opioid analgesics are necessary. Tapentadol is administered every 4–6 hours (the intervals may be shorter at the beginning of the treatment), its effect increases with the dose, the maximum dose per day should not exceed 700 mg. At high doses or in patients sensitive to μ-opioid receptor agonists, tapentadol may cause dose-dependent respiratory depression, reversible by naloxone. A very rare cases of serotonin syndrome have been noted in patients combining tapentadol and SSRIs. MAOIs should be discontinued two weeks prior to tapentadol administration. Tapentadol is not recommended shortly before delivery and during lactation. Other adverse effects include constipation, nausea, vomiting, dizziness, somnolence, and headache.

Non-traditional analgesics and adjuvant drugs

Ketamine
Ketamine was originally intended for general anesthesia and analgesic sedation in painful procedures, such as in the treatment of burns. It has been demonstrated that in small doses (1–2 mg/kg/24 h) that have no anesthetic or analgesic effects on their own, ketamine acts primarily as an antagonist at the N-methyl-D-aspartate receptors and inhibits the development of tolerance to the analgesic effects of opioids and opioid-induced hyperalgesia. Reports that ketamine significantly potentiates the effect of opioids and decreases their consumption postoperatively if a low dose (20–40 mg IV in adults) is administered during general anesthesia are only based on small samples or case studies. Despite the absence of an extensive study confirming its beneficial effect in postoperative analgesia, low doses of ketamine are often used by anesthesiologists intraoperatively.

Gabapentin
Gabapentin is an antiepileptic drug, which is also registered for the treatment of peripheral neuropathic pain. According to two recent meta-analyses, oral gabapentin in doses of 300–1200 mg administered several hours before the surgical procedure decreases acute postoperative pain by 20–64%, reduces the consumption of analgesics, the incidence of postoperative delirium in the elderly, the incidence of nausea and vomiting and may inhibit urinary retention and reduce the incidence of opioid-induced pruritus. On the other hand, gabapentin causes sedation and dizziness, and the expected long-term benefit in terms of reducing the incidence of long-term or chronic pain has not been confirmed. A series of studies have been conducted with controversial results, but in meta-analyses the use of gabapentin is currently not recommended.

Pregabalin
Pregabalin is an antiepileptic drug derived from gabapentin that is also used to treat neuropathic pain. In a 2009 review article, the results of its effectiveness in acute postoperative pain management were inconclusive (positive effect compared to placebo was reported in about 60 percent of the studies), and no effect on reducing the incidence of chronic postoperative pain was demonstrated. In comparison to routinely used medication, pregabalin does not seem to provide any significant benefit to patients after surgery, and its use in this indication is not recommended.

Alpha-2 agonists
This is another group of drugs registered for indications other than the treatment of postoperative pain, which are, however, used in clinical practice, mainly by anesthesiologists. Since this is not an approved indication and since their effect has not been documented in detail, this group of drugs is usually not recommended in postoperative pain management, with the exception of clonidine in locoregional anesthesia techniques and dexmedetomidine for analgosedation in intensive care unit patients.

Clonidine
Soon after its registration as an antihypertensive agent, anesthesiologists started to use clonidine primarily as an adjuvant to local anesthetics (see section 6.3.2.5). A systemic administration of 1–2 mcg/kg of clonidine to potentiate the effects of anesthetics and analgesics has been studied. However, there is not enough evidence in the literature for a routine use of clonidine.

Dexmedetomidine
Dexmedetomidine is a highly selective alpha-2 agonist that inhibits the release of norepinephrine in the central nervous system. Dexmedetomidine is a unique agent that is used in intensive care unit patients. It exerts a mild analgesic and sedative effect, improves the quality of analgesia and anesthesia, reduces opioid consumption, inhibits postoperative nausea and vomiting, postoperative shivering and reduces the incidence of postoperative delirium. Numerous studies have shown that dexmedetomidine alone induces analgesia and sedation without respiratory depression. When administered in an infusion, dexmedetomidine produces sedation and analgesia that is sufficient in approximately 60 percent of intensive care patients. If additional analgesic is required, its dose can be significantly reduced. For example, patients on dexmedetomidine had a 50 percent lower consumption of morphine after surgery. The main adverse effects are bradycardia and hypotension. Ventilated patients are given an infusion at an initial rate of 0.7 mcg/kg/h, which can be later adjusted as needed between 0.2 and 1.4 mcg/kg/h. As there is not enough evidence on the efficacy of dexmedetomidine in postoperative analgesia, it is not routinely recommended.

Lidocaine
Lidocaine is a local anesthetic that produces an analgesic effect after systemic administration, presumably by blocking sodium channels in peripheral nociceptors. In addition, lidocaine shortens postoperative ileus and has a favorable effect on the healing of burns. The initial dose can be 1.5–1.0 mg/kg in a short-term infusion before surgery, followed by a continuous infusion of approx. 0.02 mg/kg/min with varying duration. According to the available studies, the main benefit is observed in patients undergoing surgical procedures on the gastrointestinal tract in the abdominal cavity, where lidocaine potentiates analgesia, accelerates return of bowel functions and shortens the length of stay in the intensive care unit. Nevertheless, lidocaine is not currently recommended as a routine part of treatment and further studies are needed to confirm its efficacy. Its benefits in other indications are obvious.

Nefopam
Nefopam is a centrally-acting non-opioid analgesic whose mechanism of action is not fully understood. It does not affect COX, but inhibits the reuptake of serotonin, dopamine, and norepinephrine. The analgesic effect of a 15–30 mg dose is equivalent to 50–100 mg of pethidine. Unlike pethidine, nefopam does not have an antagonistic effect with 5-HT3 antagonists (setrons). The recommended initial dose is 20 mg in a short-term intravenous infusion about 20 minutes before the end of surgery, and then every 6 hours, or followed by a continuous administration to a maximum dose per day of 80 mg. The adverse effects of nefopam include sweating, nausea, confusion, seizures, tachycardia, and palpitations.

Corticosteroids
Glucocorticoids are COX-2 inhibitors that also have many effects on the synthesis of prostaglandins, which explains their mild analgesic effect. The onset of action is several hours after administration, thus, preoperative administration is preferred. The dose of dexamethasone is between 4–16 mg IV. This scheme is already recommended before certain surgical procedures (hemorrhoids), whereas in others (breast surgery, hernia repair) it is not recommended. Ironically, this is supposedly due to unproven efficacy– see PROSPECT, despite the fact that many studies demonstrating the analgesic effect of corticosteroids were conducted on non-cosmetic breast surgery. Besides having a mild analgesic effect, dexamethasone is routinely used for its antiemetic effect. The safety of higher doses is questionable, and dexamethasone failed to show any preventive effect on chronic postoperative pain. Other corticosteroids seem to have less of an effect. Methylprednisolone at a dose of 30–125 mg IV also produces mild analgesia, study on the effect of 50 mg of prednisone PO showed no effect on the intensity of postoperative pain.

Ondansetron
Ondansetron is a highly potent antiemetic from the group of 5-HT3 antagonists, which is used in the perioperative period to prevent nausea and vomiting, usually induced by opioids. The dose in adults is 4 mg IV or IM, the dose in children is 0.1 mg/kg, to a maximum dose per day of 4 mg IV or IM. Headache is the most commonly reported side effect. Caution! Ondansetron may reduce the analgesic effect of tramadol.

Naloxone
Naloxone is a pure opioid antagonist. It must be available at every facility where strong opioid analgesics are used to reverse the potential respiratory depression caused by opioid overdose. Naloxone given intravenously has a rapid onset of action (1–2 minutes), after intramuscular administration the onset of action is approx. 2–5 min. The elimination half-life is 1–2 hours, but the clinical effect in morphine overdose is usually shorter than one hour. In newborns, the elimination half-life is about 3 hours. After intramuscular administration, the effect wears off more slowly (specific data is not available). The main side effect is the reversal of analgesia with all its consequences. Naloxone may cause withdrawal syndrome in patients on chronic opioid therapy, and the administration of naloxone during delivery to mothers addicted to opioids is not recommended. The dose in children is 0.01 mg/kg. In adults, fractional doses of 0.1 g

IV, or 0.4 mg IM are used. In the differential diagnosis of opioid overdose, there is no point in increasing the dose of naloxone above 10 mg; if it does not lead to the reversal of CNS and respiratory depression, it is not an opioid overdose. Increasing the dose of naloxone does not extend its antagonistic effect. In morphine overdose, when the effect of naloxone wears off, another respiratory depression is likely to follow.

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6.3 Locoregional methods of analgesia

6.3.1 Introduction

As has been shown in the introductory chapters of this book, uncontrolled postoperative pain adversely affects respiration, circulation, gastrointestinal functions, metabolism,

wound healing, etc. This is particularly evident in patients undergoing major abdominal and thoracic procedures, as well as extensive orthopedic surgery. Postoperative pain management with locoregional anesthesia techniques is a highly effective solution. According to many studies, these methods are more effective (lower pain score) and at the same time reduce the incidence of adverse effects associated with systemic analgesics. Pain management using locoregional anesthesia techniques can also influence the final outcome of the surgical procedure (e.g. range of motion in the joint after surgery).

Inadequate postoperative analgesia probably contributes to the transition of acute postoperative pain to chronic pain. In this context, breast surgery, thoracotomy, cholecystectomy, inguinal hernia surgery, and amputation surgery are often mentioned. In comparison with systemic analgesia, locoregional techniques provide additional benefits. With proper timing and execution, these methods may reduce the risk of pain chronification.

6.3.2 Pharmacology of regional analgesia

Local anesthetics

Local anesthetics – general characteristics

A local anesthetic is a drug that blocks the formation and propagation of the action potential on the neuronal cell membrane (generally, in all excitable tissues) by affecting the permeability of the membrane. There are several mechanisms causing this effect. The most important one is binding to sodium channels. In the course of an action potential, sodium ions enter the cell and the plasma membrane depolarizes. Local anesthetics bind to voltage-gated sodium channels from the inner side of the membrane, block the channels, thus stabilize the membrane and inhibit the formation of an action potential. Local anesthetics are only able to bind to channels in the open state.

Sensitivity to local anesthetics differs depending on the type of nerve fibers. In general, thin fibers are more sensitive. With the same diameter, a myelinated axon will be blocked earlier than an unmyelinated one. Indeed, thin autonomic and sensory A-delta and C fibers carrying pain and temperature are blocked first. Only then thicker A-alpha, A-beta, and A-gamma fibers conveying touch, pressure, proprioception, and motor function are inhibited. Clinically, a complete interruption of conduction in a mixed nerve manifests as a loss of sensitivity to pain, temperature and touch, loss of proprioception and muscle tone.

The local anesthetic molecule consists of a hydrophobic part (usually a benzene ring) and a hydrophilic part (usually a tertiary amine). Both parts are linked by an intermediate chain containing an amide or ester bond. Based on the type of bond, local anesthetics are divided into two basic groups with a number of different properties.

Table 6.2 Properties of the two basic groups of local anesthetics

Properties	Amino-amides	Amino-esters
Metabolism	slow (liver)	rapid (plasma cholinesterase)
Systemic toxicity	higher	lower
Risk of allergy	minimal	high (due to the addition of PABA)
Stability of the solution	stable	rapid degradation (heat, light)

Note: PABA – para-aminobenzoic acid

The anesthetic potency is mainly subject to its *liposolubility* (usually expressed as a water partition coefficient). In other words, it is determined by the ability of the local anesthetic molecule to pass through the cell membrane (hydrophobic medium). The speed of onset of the blockade is influenced by many factors, the most important being the *pKa* coefficient. This coefficient expresses the relationship between a non-ionized form of the local anesthetic and its ionized form. Local anesthetics with a *pKa* closest to the physiological pH will have a higher concentration of the non-ionized form in tissues, penetrate the cell membrane more easily and generally have a faster onset of action. The duration of the blockade is determined primarily by binding to plasma proteins, as well as by the lipophilicity of the LA and by added vasoconstrictors.

Local anesthetics – overview

Procaine

Procaine is an amino-ester local anesthetic that was also used for intravenous infusions due its very low toxicity. Its use in locoregional anesthesia is very limited. There is a real risk of anaphylaxis (PABA). Currently, its derivative chloroprocaine is entering the market again.

Lidocaine

Lidocaine is the most widely used short- to intermediate-acting local anesthetic of the amino-amide type with low toxicity. 0.5–1% lidocaine is used in infiltration anesthesia, 1–2% for peripheral nerve blocks, and 1–2% for epidural blockade. There are several available forms: injections, patches, gel, or an aerosol spray. Lidocaine is commonly used together with epinephrine, which prolongs its effect and reduces its plasma levels.

Articaine

Articaine is a short-acting amide-type local anesthetic with a very rapid onset of action and low toxicity. Unlike other anesthetics, artcaine contains a thiophene ring in the lipophilic part of the molecule. Articaine is used in the same concentrations and indications as lidocaine. It is slightly more potent and less toxic than lidocaine. Motor blockade is very fast and intense.

Bupivacaine

Bupivacaine is a long-acting local anesthetic of the amide type with higher potency than lidocaine and more pronounced cardiotoxicity. Bupivacaine is a racemic mixture of D and S enantiomers, with S form (levobupivacaine) being less toxic. The onset of action is very slow, but the duration of action may in some cases extend to many hours. 0.25% bupivacaine is used for infiltration anesthesia, 0.375–0.5% for peripheral nerve blocks, 0.5% for epidural anesthesia, and 0.1–0.25% for analgesia. Isobaric and hyperbaric solutions are available for intrathecal use.

Levobupivacaine

Levobupivacaine is the S-enantiomer of bupivacaine with a slightly lower anesthetic potency and lower cardiotoxicity. The concentrations used in clinical practice are identical to those of bupivacaine. Levobupivacaine is also available in 0.75% to achieve

a deeper level of blockade in lumbar epidural anesthesia. Motor blockade is less pronounced and of shorter duration than with bupivacaine.

Ropivacaine
Ropivacaine is chemically related to bupivacaine, with a slightly lower anesthetic potency and lower cardiotoxicity. It is available as a 0.2%, 0.5%, 0.75%, and 1% solution. Motor blockade is less marked and of a shorter duration than with bupivacaine.

The last two local anesthetics in the list are chiral substances. Their enantiomers differ in the potency/cardiotoxicity ratio. Their considerably more favorable potency/cardiotoxicity ratio is beneficial in techniques requiring higher doses of local anesthetics.

Table 6.3 Properties and maximum dosage of local anesthetics

Local anesthetic	pKa	Relative liposolubility	Relative potency	Binding to plasma proteins	Maximum dose
Procaine	8.9	1	1	6%	7 mg/kg
Lidocaine	7.7	150	2	65%	4.5 mg/kg
Lidocaine with epinephrine	7.7	150	2	65%	7 mg/kg
Bupivacaine	8.1	1000	8	95%	2.5 mg/kg, not exceeding 175 mg in adults
Bupivacaine with epinephrine	8.1	1000	8	95%	not exceeding 225 mg in adults
Ropivacaine	8.1	400	6	94%	3 mg/kg
Levobupivacaine	8.1	1000	8	95%	2.5 mg/kg

Note: The above mentioned maximum dosage may, under certain circumstances, lead to a severe toxic reaction! Always take into account the patient's condition and the site of administration! With the same dose, plasma levels decrease in the following order: intravenous> intratracheal> intercostal> caudal> paracervical> epidural> brachial plexus> sciatic> infiltrative administration.

Toxic and allergic reactions

Systemic toxicity of local anesthetics

Should safe plasma levels of local anesthetics be exceeded, signs of systemic toxicity develop. With increasing plasma levels, neurotoxic symptoms are the first to appear, followed by cardiotoxicity which may be life-threatening. Cardiac arrhythmias with cardiovascular collapse occur at levels approximately three times as high as those causing seizures. However, this ratio is different for different anesthetics. Always remember that monitoring the neurological status of the patient receiving local anesthetics (by means of an informal talk, which requires the patient to respond regularly) can often prevent a non-resuscitable cardiac arrest.

Allergic reaction to local anesthetics

True allergic reaction to local anesthetics is very rare. Many of the reported reactions have a different underlying pathophysiological mechanism (systemic toxicity, vagal syncope). Allergic reactions are, for the most part, associated with amino esters (para-aminobenzoic acid derivatives). Due to their different structure, there is no allergic cross-reactivity between the two groups.

The diagnosis is based on the presence of the following symptoms, in order of severity: hypotension, shock, cardiac arrest (88%), erythema (45%), bronchospasm (36%), angioedema (24%), and other skin symptoms. The differential diagnosis should include: primary cardiac cause of circulatory failure, asthma, pneumothorax, etc.

Table 6.4 Diagnosis and treatment of toxic reactions

Severity of the reaction	Symptoms	Treatment
Mild reaction	Metallic taste in the mouth, circumoral paresthesia, tinnitus, blurred vision, agitation, motor restlessness, muscle twitching	100% oxygen, low doses of midazolam (1–5 mg), Mind hypoxia and acidosis due to hypoventilation
Moderate reaction	Tonic-clonic seizures Loss of consciousness	Thiopental, benzodiazepines to treat seizures, intubate with muscle relaxation if signs of hypoxia and hypoventilation develop, consider Intralipid 20% 1.5 mL/kg IV over 1 min and then 0.25 mL/kg/min
Severe reaction	Respiratory arrest Cardiac arrhythmias, hypotension Cardiac arrest	Previous measures + CPR (long-term) Intralipid 20% 1.5 mL/kg IV over 1 min and then 0.25 mL/kg/min Catecholamines according to CPR guidelines

Notes: Every health care facility using long-acting local anesthetics should have a 20% intravenous lipid emulsion available among other resuscitation medications (lipid rescue). Due to its concentration, the lipid content in propofol solution is not an adequate substitute.

The duration of the CPR is not subject to commonly accepted guidelines. Restoration of cardiac activity often requires a very long resuscitation. A successful use of extracorporeal circulation has been reported.

Immediate measures

Discontinue the administration of any potential antigens
Call for help
Maintain an open airway, administer 100% oxygen
Place the patient in horizontal position with elevated lower limbs
Administer IV epinephrine in 50 mcg boluses until the pulse is palpable and bronchospasm is relieved (alternatively, 0.5 mg can be administered IM)
Administer fluids quickly (crystalloids are preferable, colloids are also possible)

Follow-up treatment

Antihistamines: chlorphenamine 10–20 mg IV, slowly
Corticosteroids: hydrocortisone 100–300 mg IV
Catecholamines: if circulatory instability persists
Epinephrine: 0.05 mcg/kg/min or
Norepinephrine 0.05–0.1 mcg/kg/min
When in doubt about clear airway, intubate and temporarily use mechanical ventilation
If bronchospasm persists, administer inhaled beta-agonists
If the patient develops a very severe metabolic acidosis, administer bicarbonate

Collect 3 blood samples (immediately, after 1 hour and after 6–24 hours) to measure tryptase levels and one urine sample to measure methylhistamine.

6.3.3 Infiltration analgesia

This technique is used extensively in a number of surgical procedures. A local anesthetic is usually applied by the surgeon at the end of the procedure, ideally into the various layers when closing the wound. It is a typical infiltration anesthesia using long-acting local anesthetics, often at the upper limit of the recommended dose range. Taking into account the contraindications, vasoconstrictors can be added. There is no evidence of a negative influence of local anesthetics on wound healing or on the incidence of infectious complications. It is an extremely effective, but unfortunately, a short-term postoperative pain management technique.

Continuous incisional infusion of local anesthetic is a technique based on a repeated instillation of local anesthetics into the wound via a catheter inserted by the surgeon prior to wound closure. 18G or 16G epidural catheters with a bacterial filter are commonly used. Local anesthetics are administered in boluses, continuously by a delivery system, or using a PCA system with an elastomeric pump. This method of analgesia is particularly suitable for surgery on the lower abdomen with little traumatization of the abdominal organs and peritoneum (simple hysterectomy from a Pfannenstiel incision).

6.3.4 Neuraxial techniques in analgesia

Introduction – theoretical assumptions

Neuraxial anesthesia/analgesia involve techniques of administration of a local anesthetic (and adjuvants) into the spinal canal. The target area of the anesthesiologist is either the intrathecal space (spinal anesthesia), or epidural space (epidural and caudal anesthesia). These techniques generally achieve a bilateral sensory, motor, and autonomic nerve blockades of a varying extent (level).

The **maximum level of sensory blockade** (MLSB) is the cranial spread of an intrathecally administered anesthetic (and its neuronal uptake) in a sufficient amount to produce an identifiable sensory blockade. Logically, this concept is used to evaluate spinal anesthesia.

The **extent of the blockade** is defined by the caudal and cranial spread of the local anesthetic in a clinically significant amount to produce an identifiable sensory blockade. This concept is usually used to characterize epidural block.

Somatosensory blockade is the most important constituent of a successful surgery and adequate postoperative pain management. When considering the extent of the blockade, it is necessary to take into account the innervation of the skin and periosteum. In segmental epidural blockade, the different distribution of the periosteal and skin innervation may clinically manifest. The extent and level of the blockade is usually assessed by means of tactile or painful stimuli.

Motor blockade can significantly affect the course of the surgical procedure – especially from the perspective of the surgeon ("tension free" techniques in inguinal hernia repairs, hip joint prosthetics…). Motor blockade is usually 2 segments below the level of the sensory blockade. The extent, level and intensity of the motor blockade is evaluated according to the Bromage score.

Autonomic nerve blockade mainly applies to sympathetic nerve blockade, which is responsible for a number of potentially beneficial cardiovascular, respiratory, gastrointestinal, and metabolic effects. Only the sacral portion of parasympathetic fibers may be influenced as well.

Table 6.5 Sensory innervation of the trunk with respect to surgical incision

Lower midline laparotomy	T 10–11
Upper midline laparotomy	T 6–10
Subcostal incision	T 7–10
Lumbotomy	T 9–11
Pfannenstiel incision	T 11–12
Sternotomy	T 2–6
Thoracotomy	according to the intercostal space

Table 6.6 Autonomic innervation of the organs – sympathetic nervous system

Heart	T 1–4	Pancreas and spleen	T 6–10
Lungs	T 2–4	Kidneys and ureter	T 10–L 2
Esophagus	T 5–6	Adrenal gland	T 8–L 1
Stomach	T 6–10	Testes and ovaries	T 10–L 1
Small intestine	T 9–10	Urinary bladder	T 11–L 2
Colon	T 11–L 2	Prostate	T 11–L 1
Liver and gallbladder	T 7–9	Uterus	T 10–L 1

Single-injection techniques can provide high-quality postoperative analgesia, but unfortunately only for a very limited period of time. In postoperative pain management, continuous epidural (or caudal) analgesia plays a dominant role.

Continuous epidural blockade

Continuous epidural blockade in thoracic and abdominal surgery

Continuous thoracic epidural analgesia is irreplaceable in extensive thoracic and abdominal surgical procedures. When comparing intrathecal and epidural techniques, the movement of the local anesthetic in the epidural space is less defined in terms of space, however, its predictability and thus the controllability of the extent of the blockade is more reliable. In high thoracic epidural anesthesia (TEA), a greater part of the local anesthetic spreads in the caudal direction, while in low TEA, the flow is mostly in the cranial direction. This is mainly due to the caudal expansion of the epidural space (C5 1–1.5 mm, T6 2.5–3 mm, L2 5–6 mm). *The site for introducing low TEA should correspond approximately to the innervation of the center of the surgical incision. With high TEA, it should correspond to the innervation of the upper pole of the incision.* When applying this basic rule, it is always necessary to take into account the autonomic innervation of the organ operated on.

This proper segmental administration of the epidural blockade seems to be vital. Local anesthetics should be administered before the induction of general anesthesia and the doses of general anesthetics and opioid analgesics should be reduced accordingly. Continuous postoperative epidural analgesia should last for at least 72 hours and should be used for early rehabilitation. Numerous studies have shown that the evaluation of the influence of analgesia alone (taken out of the context of the whole perioperative care) on the total outcome is very problematic.

Lumbar epidural blockade for abdominal and thoracic surgical procedures is a wrong technique. Anesthesiologists use it out of fear of the difficulty of thoracic epidural puncture, of major and persistent hypotension if sympathetic fibers are blocked and out of fear of possible neurological complications. Lumbar epidural anesthesia is more difficult to perform for higher thoracic segments, even when high doses of local anesthetics are used. Postoperative pain management is burdened with more frequent systemic opioid interventions and lower limb motor blockade is often poorly tolerated. The sympathetic nerve blockade affects lower limbs. Vasoconstriction triggered by baroreceptors is maintained cranially from the blockade with all the potentially dangerous effects on the myocardium.

Continuous epidural blockade in lower limb surgery

Continuous epidural blockade can provide better analgesia for these procedures than systemic analgesics. This fact has been confirmed by numerous studies, which have also shown that these patients are discharged from hospital with better functional outcome of surgery (or need fewer days of rehabilitation to achieve the same range of motion in the joint). In these procedures, proper placement is crucial. Some procedures take place in a relatively narrow innervation area. With the catheter introduced at the proper level, a slower rate of local anesthetic infusion is sufficient. The following table offers guidance on the proper level of the epidural catheter in lower limb surgery.

Table 6.7 Ideal position of the epidural catheter in lower limb surgery

Surgical procedure	Skin incision	Periosteum	Recommended position of the epidural catheter
Hip joint	L1–L3	L3–S1	L2
Knee joint	L3–L4	L3–L5	L3
Ankle, foot	L4–L5	L4–S2	L5

Practical aspects of performing continuous epidural blockade

Procedure

An epidural puncture is performed under strict aseptic conditions with the patient lying on the side or sitting. Midline or paramedian (preferably in the thoracic region) approach is used. The epidural space is identified using loss of resistance or hanging drop techniques and an initial test dose of a local anesthetic is administered. Then the epidural catheter is introduced 2–5 cm into the epidural space. If the catheter is inserted further, there is a greater risk of it moving into the paravertebral space and kinking. Then another test dose is administered to rule out intrathecal position of the catheter. The catheter is connected to a bacterial filter, fixed and covered with a sterile dressing, ideally a transparent film (Tegaderm), allowing visual inspection of the injection site.

If this type of analgesia is to be provided for an extended period of time, the catheter should be tunneled.

Continuous epidural blockade has the following **contraindications**:

- local infection and severe sepsis
- coagulation disorders
- uncorrected hypovolemia, shock state
- patient refusal
- insufficiently qualified personnel

Continuous epidural analgesia might be problematic in some neurological diseases (multiple sclerosis). There are no proven negative effects of a continuous epidural analgesia on the course of these diseases. However, it requires an individual approach with rigorous monitoring of the neurological status and its documentation. Any deterioration of the condition may be given in connection with the block.

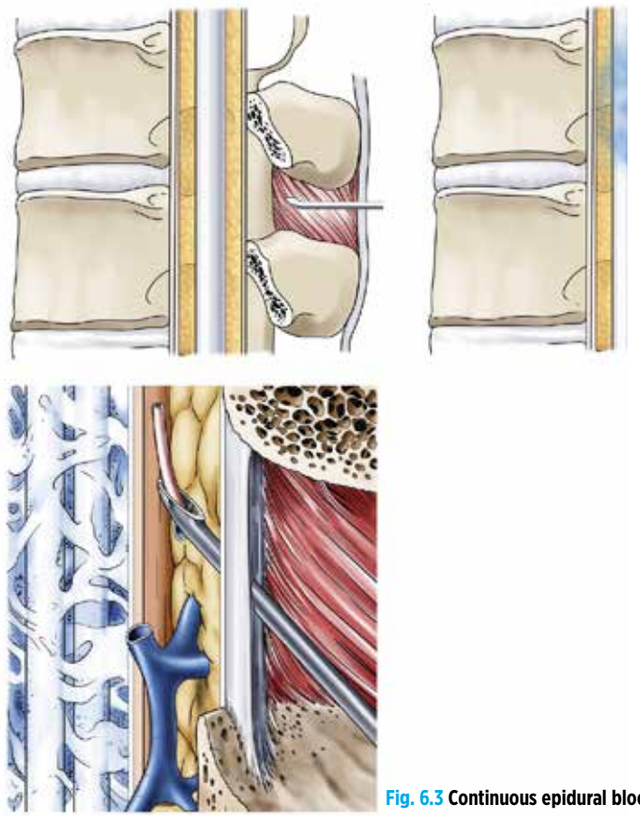

Fig. 6.3 Continuous epidural blockade

Management and monitoring of analgesia

In accordance with the local protocol, every patient with an inserted epidural catheter should be monitored using a "*Continuous epidural analgesia record sheet*", which should, apart from the usual identification data, include:

- date and time of catheter insertion
- its position, length in the epidural space, and the depth of the insertion (measured from the skin)
- time of administration and size of the test doses, including effect
- prescription for epidural infusion with a defined max. and min. infusion rate
- prescription for a "rescue" treatment, if the effect is insufficient (or refer to the protocol)
- record of regular checks, or dressing change
- record of dose change and its reason
- date and time of catheter removal

The basic scheme for continuous epidural infusion is:
bupivacaine 0.1% + fentanyl 2-5 mcg/mL, rate: 5-12 mL/h
(fentanyl may be replaced with sufentanil 0.5–1 mcg/mL, or morphine 0.05–0.1 mg/mL)

It is not entirely clear whether the effect of this combination is additive or synergistic (different results in various studies). However, this combination is beneficial, as it provides better analgesia, and the dose of the local anesthetic can be reduced. The incidence of side effects may or may not be reduced.

The infusion rate can be reduced in procedures where pain is localized in a few adjacent segments. On the other hand, it is often necessary to increase the concentration up to 0.25%. Especially on day 0 after a very painful surgical procedure, it is important to remember "rescue" procedures in the protocols (bolus doses, increasing the rate or concentration). The administration of systemic opioids in patients with a continuous epidural analgesia should be strictly reserved for closely monitored beds. By contrast, the concurrent initiation of systemic analgesic therapy with non-opioid analgesics (paracetamol) is included in most protocols.

Space and personnel requirements for postoperative continuous epidural analgesia should be provided for by local regulations and protocols. After major surgical procedures on the chest and upper abdomen with an introduced high thoracic epidural catheter, it is advisable to provide analgesia on a monitored bed during the first 12 to 24 hours. A stable patient with a functional epidural analgesia can be moved to a standard ward, provided that regular checks of functionality are carried out and early signs of potential complications are monitored. This can be done either by trained personnel of the department, or by a team providing acute pain service in the hospital. In addition to regular monitoring, a patient with continuous epidural analgesia should be checked upon every day by a specialist (preferably the anesthesiologist who performed the block, or a member of the acute pain service team), who should record it in the documentation.

Cessation of epidural infusion. The duration of the epidural catheter placement depends on the indication (nature and location of pain) and on the possibility of switching to sufficient systemic analgesia. After most surgical procedures, it is usually 72 hours, as an increasing duration is associated with an increased risk of infectious complications. The day before the cessation, the dosage is gradually reduced. The catheter should be removed by a specialist familiar with potential complications (ideally the anesthesiologist who introduced the catheter). Contraindications for catheter removal are identical to those for its placement (in terms of hemostasis and medication that affect it). Up to 50% of epidural hematomas result from catheter removal. For this reason, early signs of complications should be monitored in the next few hours.

Common complications of continuous epidural analgesia

Hypotension

Hypotension is reported in 3–30% of patients. Its incidence and intensity is significantly affected by the fluid regime used in the health care facility in the early postoperative days. Hypotension responds very well to fluid loading and a small dose of ephedrine. In some cases, only reducing the dose of the local anesthetic helps. Other possible (surgical) causes of hypotension should be kept in mind as well.

Motor blockade

Motor blockade is reported in 2–3% of patients. It usually responds very well to dose reduction (especially in terms of concentration) of local anesthetics. Impaired mobility may result in the formation of pressure sores in predisposed patients. It may be an early sign of a serious complication (see below).

Pruritus

Pruritus is a common effect of opioids administered into the intraspinal space with the incidence of up to 60%. It is reported only in 15–18% of patients with epidural blockade without opioids (similarly to systemic opioids). Pruritus is most likely caused by central irritation of the "itch" center in the CNS. This mechanism has nothing to do with histamine. It is more common with epidural morphine than with fentanyl. If treatment is required, usually a small dose of naloxone helps.

Urinary retention

Urinary retention may be caused both by opioids (more common with neuraxial administration regardless of the dosage than with systemic administration) and local anesthetics. In some cases, a small dose of naloxone might help. Most patients undergoing major surgical procedures are catheterized. It is usually poorly tolerated in minor procedures in young men, which may be a reason for its refusal.

Severe complications of continuous epidural analgesia

Severe complications of continuous epidural analgesia are rare, but if they do occur, they may have devastating consequences for the future life of the patient and, by extension, for the professional life of the anesthesiologist. Every health care facility using neuraxial techniques should have a protocol for an early diagnosis and treatment of severe complications of neuraxial blocks. It should include:

1. Protocol for monitoring early signs of severe complications and their documentation
2. Clearly defined diagnostic procedure (availability of imaging techniques)
3. Clearly defined therapeutic procedure (availability of neurosurgery or spinal surgery in the vicinity).

Table 6.8 Severe complications of neuraxial blocks

	Epidural abscess	Epidural hematoma	Anterior spinal artery syndrome
Age	any	50% > 50 years	old age
Medical history	immunosuppression	anticoagulants	arteriosclerosis/hypotension
Onset of action	1–3 days	sudden	sudden
General symptoms	temperature, general symptoms of infection, back pain	sharp pain in the back, or into the limbs	none
Sensory symptoms	none, or paresthesia	mild and late	mild and late
Motor symptoms	flaccid paresis, later spastic	flaccid paresis (often as the first symptom)	flaccid paresis
Segmental reflexes	sometimes increased, then absent	absent	absent
MRI/CT/myelogram	signs of compression	signs of compression	none
CSF	signs of inflammation	none	none
Blood	inflammatory markers	coagulation disorders	none

If an expansion of the spinal canal with neurological symptoms develops, conservative therapy does not help. Decompression laminectomy should be performed within 8 hours of symptom onset. After 14 hours of symptom onset, paraplegia is usually irreversible.

6.3.5 Peripheral blockades in analgesia

Peripheral nerve block techniques can play a very important role in acute postoperative pain management. Especially from the point of view of safety, peripheral blockades are preferable to systemic analgesia and neuraxial blockades.

Peripheral nerve blockades can be used for postoperative analgesia in two principal ways:

1. as a single-injection peripheral nerve blockade to prolong the effect of local anesthetics
2. as a continuous peripheral nerve blockade to extend the effect by repeated administration

Many studies have shown that postoperative pain management using locoregional anesthesia techniques is superior to systemic analgesia in patients undergoing limb surgery. In terms of analgesia, peripheral nerve blockades are comparable to continuous epidural analgesia and have a lower risk of adverse effects and complications.

Single-injection peripheral nerve blockades

The following methods are used to extend the effect of single-injection nerve blockades into the postoperative period for as long as possible:

1. long-acting local anesthetics (bupivacaine, ropivacaine, levobupivacaine)
2. substances prolonging the effect of local anesthetics (epinephrine)
3. adjuvants with a presumed or proven local anesthetic effect (clonidine)

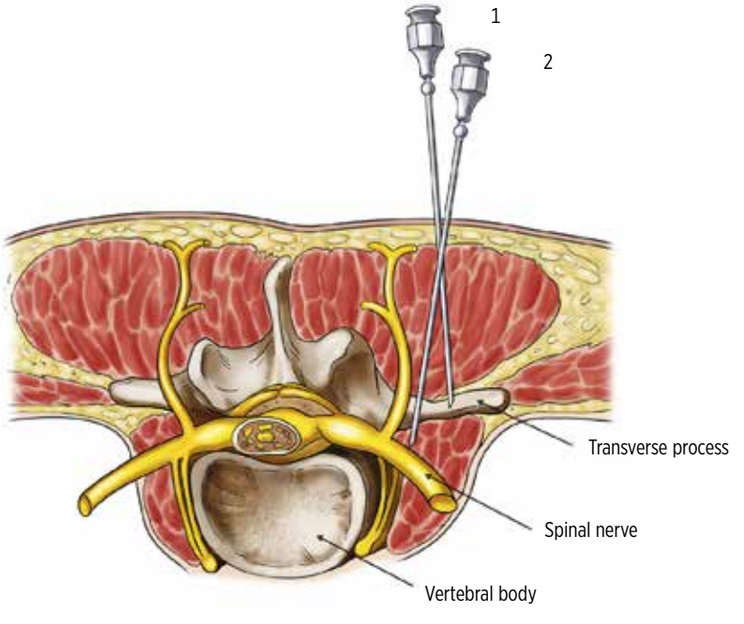

Fig. 6.4 Paravertebral blockade

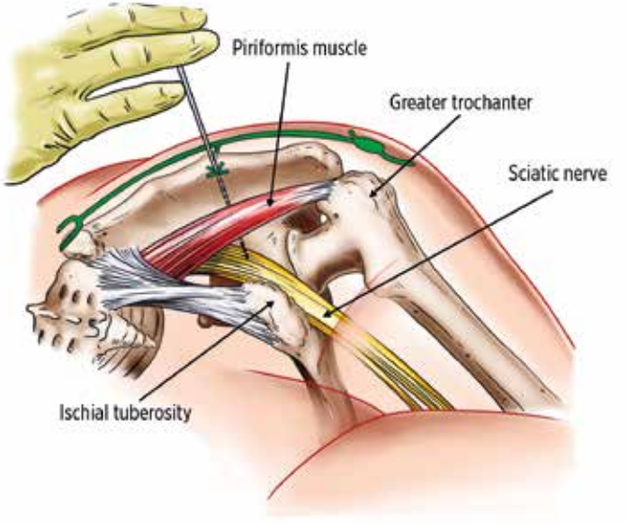

Fig. 6.5 Sciatic nerve blockade

As for peripheral nerves and plexuses, a combination of long-acting local anesthetics and certain adjuvants can provide adequate analgesia for 12–24 hours, which is often sufficient to cope with the most painful postoperative hours. This is smoothly followed by systemic analgesia with NSAIDs or paracetamol, which is usually sufficient. This applies to most minor and intermediate surgical procedures in orthopedics and traumatology. Currently, this analgesic approach is more and more appreciated, as analgesia is provided by a single physician with a single intervention and for a very long time. Any potential risks of analgesia are bound to the time of the administration of the blockade, which is usually performed by an experienced specialist. Thus, there are no such risks as with systemic and continuous neuraxial analgesia, such as mistaking the medication on the ward, the site of administration, technical failures (dispensers), risks associated with improper monitoring of vital signs … Peripheral nerve blockade for analgesia combined with general anesthesia is a perfectly legitimate technique. The combination with general anesthesia is usually used for patient comfort (forced position for a long time…). Therefore, it is not perceived as a failure of locoregional anesthesia.

A detailed description of the various techniques is beyond the scope of this book. The following table contains a list of peripheral nerve blockades with possible indications in the treatment of postoperative pain. This list is far from being complete and the choice depends on the preferences of the anesthesiologist. Currently, conventional neurostimulation techniques are being replaced with ultrasound guidance, thus the traditional classification has rather a didactic purpose. Access to the nerve or plexus is selected based on the optimal availability and quality of ultrasound imaging. Similarly, the dose of local anesthetics depends on their optimal distribution controlled by the ultrasound.

Always remember that:

- dose of local anesthetics is approximate, always take into account the patient's general condition
- concentrations in the analgesic indication are within a wide range (0.125–0.5%). Higher concentrations provide a longer duration of the blockade, however, they are associated, associated with an unpleasant motor blockade lasting for several hours.
- for the purpose of overall well-being of the patient undergoing surgery on distal limbs, motor activity of proximal limbs should be maintained (distal approaches are preferred to maintain the mobility of the shoulder, hip…)
- in procedures on the lower leg/forearm diaphysis, always discuss the diagnostic options of a compartment syndrome with the surgeon beforehand

Table 6.9 Peripheral nerve blockades in postoperative pain management

Surgical procedure	Peripheral nerve blockade	Dose of local anesthetic, comment
Carotid artery surgery, thyroid, other procedures on the neck and external ear lobe	deep cervical plexus blockade superficial cervical plexus blockade	10–15 mL of LA
Outer third of the clavicle	interscalene blockade	20 mL of LA, preferably in combination with superficial cervical plexus blockade
Shoulder joint, proximal humerus	interscalene blockade supraclavicular blockade	20 mL of LA is usually sufficient in both procedures
Shoulder joint	suprascapular nerve blockade	10–15 mL of LA
Arm	interscalene blockade supraclavicular blockade	30 mL of LA 20 mL of LA
Elbow	infraclavicular blockade MHB, axillary blockade	25–30 mL of LA 7–10 mL of LA to each nerve
Forearm *(compartment syndrome!)*	infraclavicular blockade MHB, axillary blockade	25–30 mL of LA 7–10 mL of LA to each nerve
Wrist, hand	MHB, axillary blockade nerve block at the elbow	7–10 mL of LA to each nerve 7–10 mL of LA to each nerve
Mastectomy	paravertebral block at T1–5	5–7 mL of LA for each segment, max. innervation T3
Thoracotomy	paravertebral block according to the intercostal space	5–7 mL of LA, preferably together with catheter placement
Cholecystectomy	paravertebral block at T6–9	5–7 mL of LA for each segment
Nephrectomy using lumbotomy	paravertebral block at T9–11	5–7 mL of LA for each segment
Inguinal hernia repair	paravertebral block at L1, T12	5–7 mL of LA for each segment, one larger bolus in one segment can be administered
Periumbilical procedures	rectus sheath blockade	10–15 mL of LA
Lower laparotomy, appendectomy, herniotomy	TAP blockade	20 mL on each side, useful when epidural blockade cannot be administered
Hip joint	psoas compartment blockade, fascia iliaca blockade, or "3-in-1" blockade	30 mL of LA, the blockade usually numbs only a part of the wound and relaxes a painful spasm of the quadriceps femoris muscle
Knee joint	lumbar plexus blockade + sciatic nerve blockade	25 mL of LA, lumbar plexus covers approx. 75% of the innervation of the knee 15 mL of LA
Lower leg *(compartment syndrome!)*	sciatic + saphenous nerve blockade	15–20 mL of LA 10 mL of LA, often not required for analgesia (it is only a cutaneous nerve)
Ankle, foot	sciatic + saphenous nerve blockade	15–20 mL of LA 10 mL of LA, often not required for analgesia (it is only a cutaneous nerve)

Note: MHB – mid-humeral blockade, **LA** – local anesthetic, **TAP block** – transversus abdominis plane blockade

Continuous peripheral nerve blockades

Analgesia using a continuous peripheral nerve or plexus blockade is a very elegant technique, which is used with increasing frequency. This is certainly thanks to its high efficiency, as well as low risk of severe complications. Proper and atraumatic insertion of the catheter requires a detailed knowledge of anatomy. Catheters are placed near nerve plexuses or peripheral nerves. When inserting catheters near nerve plexuses, perivascular technique is mostly used. Neural structures are part of the neurovascular bundle, enclosed by a common fibrous sheath. A local anesthetic is applied into the common sheath, thus remains distributed along the nerve to provide anesthesia/an-

algesia. When administering proximal blockades on lower limbs, we use the fact that plexuses and nerves run in muscle and fascial compartments (psoas compartment, fascia iliaca blockade). Introducing a catheter near terminal neural structures is more technically demanding.

Catheter placement techniques:
„Over the needle" – the cannula forms the outer coat of a stimulating metal needle and is advanced over the needle towards the nerve. All anesthesiologists are familiar with this technique from their everyday work in the operating room while performing venipuncture. In peripheral nerve blockades, this technique has its disadvantages. It is more commonly used for axillary approach.

„Through the needle" – the catheter is inserted inside the stimulating needle. This technique is very popular and commonly used in this indication. The currently available kits allow choosing between a common blunt-tipped stimulating needle and "pencil-point" needle. They are used on both the upper and lower limbs. For paravertebral blockade (nerve root blockade), "through the needle" technique with a Tuohy needle and an epidural catheter may be used.

Seldinger technique – a known, but less frequently used technique in this indication. It is perhaps more often used for continuous blockades on lower limbs ("3-in-1" blockade, popliteal blockade).

Combination of the first two techniques is used in several commercially produced kits. First, a plastic cannula is introduced using the "over the needle" technique, then a catheter is inserted inside the cannula.

Methods of catheter placement verification:
Ultrasound – ultrasound can monitor the position of the needle, catheter, and especially the distribution of the local anesthetic around the nerves
Stimulating catheters – enable to verify the position of the catheter tip after its placement. After locating the nerve or plexus with a stimulating needle, the stimulator is connected to the catheter.
X-ray control – enables to check the position of the catheter tip, as well as the distribution of the local anesthetic solution labelled with a contrast agent.

Basic principles allowing catheter placement:
Parallel principle – logically, it will be much easier to insert the catheter in a direction parallel with the nerve fibers. This principle works best for axillary blockade, infraclavicular blockade, certain modifications of the interscalene blockade, femoral nerve blockade ("3-in-1") or popliteal blockade. By contrast, perpendicular direction requires the catheter to turn towards the nerve (vertical infraclavicular blockade).
Proper selection of material – different types of stimulating needles (for example: Tuohy, pencil-point, …) create different directions, in which the catheter leaves the needle during its insertion. It is advisable to become familiar with this prior to catheter placement.
Dilatation of the space, into which the catheter is inserted – administration of a local anesthetic (or a solution when using a stimulating catheter) through the stimulating needle can significantly facilitate catheter placement by dilating the target space. The catheter is inserted using a constant gentle pressure without excessive force to prevent kinking. The catheter is typically placed 2–3 cm from the peripheral nerves.
Catheter fixation and care – very loose skin and subcutaneous tissue (interscalene approach) allows easy dislocation of the catheter in the perioperative and postoperative period. From this point of view, infraclavicular approach is preferable. Upon reaching the final position, fix the catheter well and use an antibacterial filter. If you plan to use the catheter for more than one week, tunnel it subcutaneously.
Proper indication – it is absolutely necessary to place the catheter near the nerve(s) responsible for the innervation of the operated area. The physician needs to know the extent of the surgical procedure, as well as skin and periosteal projections of peripheral nerves and roots.

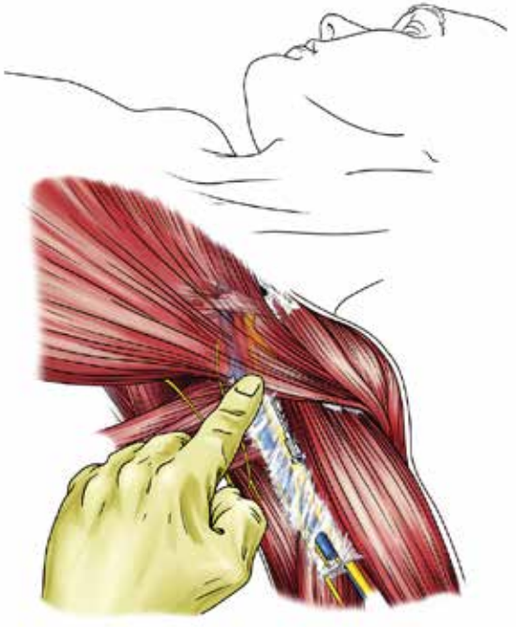

Fig. 6.6 Perivascular technique of axillary brachial plexus blockade

Dosage and administration regimens:
Analgesia can be provided in three regimens:
Bolus administration – does not limit the movement of the patient, cheap, but associated with the typical disadvantages of boluses. Long-acting anesthetics (bupivacaine 0.125–0.25%, ropivacaine 0.2%), usually in a volume of 20 mL per bolus, are used.
Continuous infusion administration – more stable and balanced analgesia, limits the mobility of the patient, short-acting local anesthetics are used.
Administration via PCA – highly preferable, allowing self-administration.

Upper limb
In terms of the parallel principle, axillary approach, certain infraclavicular approaches and a modification of the classic interscalene approach seem to be very suitable. In

general, standard approaches may be modified by slight changes in the inclination of the needle or by shifting the puncture site. By contrast, vertical infraclavicular, interscalene and posterior scalene approaches provide perpendicular access to nerves.

Lower limb
The general principles are the same as with catheter introduced to the brachial plexus. Many anesthesiologists will certainly consider these blockades controversial and prefer more common central blockades. However, a properly indicated and performed peripheral blockade on the lower limb offers many advantages.

Sciatic nerve
These techniques are used in major surgical procedures on the bones of the foot or distal lower leg, or in repeated procedures on the foot (diabetic gangrene …)
Popliteal blockade using the posterior approach is very suitable for catheter placement and probably the best option in terms of the parallel principle.
Modified Labat's approach according to Sutherland aims to insert the catheter along the nerve using the posterior approach, but with a significantly different direction of the needle. The tip of the needle is directed distally at an angle of 35–45°, towards the midpoint between the lesser trochanter and ischial tuberosity.

Lumbar plexus
Both techniques are suitable for analgesia after surgery on the knee, femur, and hip. They significantly reduce systemic analgesic requirements after major procedures (total joint replacement).
3-in-1 blockade – probably the most commonly performed blockade on the lower limb in the continuous form. Seldinger technique is used with success for catheter placement.
Psoas compartment blockade – the catheter is introduced into the psoas compartment after administering an initial bolus to rule out spinal or epidural placement of the catheter.

6.3.6 Special locoregional techniques in analgesia

Intra-articular analgesia

The effect of opioid analgesics administered into the joint has been studied primarily on knee arthroscopy. Morphine administered in this way can provide analgesia for up to 24 hours. It might also influence the development of chronic pain. During an inflammatory reaction, peripheral opioid receptors appear on afferent nerves. Despite the low absorption from the joint cavity, an overall systemic effect cannot be excluded. Local anesthetics act in a similar way, but their effect is shorter. Administration of local anesthetics into the joint after arthroscopy is a routinely used technique in day surgery.

Intrapleural analgesia

This technique was first described in the treatment of pain after a unilateral rib fracture. The pain to be treated should lie within the innervation area of intercostal nerves, which are rinsed with local anesthetics. Similar approach may be adopted to provide analgesia for open cholecystectomy. Bilateral blockade is theoretically possible, but not recommended. Obesity and a history of severe lung disease with a risk of pleural adhesions are contraindications for this technique. It is also possible to use continuous catheter technique. The patient is lying on the side and a Tuohy needle is introduced in the anterior axillary line (in one of the 3rd to 6th intercostal space). A syringe is attached to the needle (either without the plunger with fluid, or unimpeded with the plunger pulled halfway). The puncture is performed while the patient is holding breath after expiration. After penetrating the pleural cavity, the level in the syringe will drop, or the plunger will move downwards. Try to minimize the amount of air or fluid that goes through. At least 10 cm of the epidural catheter are introduced and a bolus of 15–20 mL of 0.5% bupivacaine is administered. The administration is performed slowly and the distribution of the local anesthetic can be influenced by positioning the patient. Analgesia is usually sufficient for 6–9 hours. A continuous infusion of 5–10 mL/h may follow. Alternatively, the catheter can be placed by the surgeon prior to thoracotomy closure. The risk of a clinically significant pneumothorax is minimal. A minor pneumothorax is not a problem, but beware long general anesthesia with nitrous oxide.

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6.4 Multimodal analgesia

Opioid analgesics have long been considered a gold standard of postoperative analgesia. With the introduction of new drugs, a number of studies have questioned their privileged position. Criticism has focused on two major drawbacks: firstly, the adverse effects of opioid analgesics, especially nausea, vomiting, urinary retention, and prolonged postoperative ileus, and secondly, the fact that safe doses relieve pain, but only to a certain degree. Therefore, multimodal analgesia is gaining ground – that is the use of multiple medications and various techniques.

Combination of systemically administered medications

This concept is based on the idea that the administration of analgesics from different groups will have an additive effect on the suppression of pain, which would reduce the analgesic requirement, of opioids in particular, and thus the occurrence of their adverse effects. This point is especially important, since some papers only emphasize the decrease in opioid requirement, without monitoring a reduction in the incidence of nausea, vomiting, and inhibition of intestinal peristalsis. The Oxford league table of analgesics, which is solely based on high-quality studies, states that certain COX-2 selective inhibitors or a combination of paracetamol and tramadol are more effective in the treatment of pain than the actual administration of strong opioids (Table 6.10). This table has been repeatedly challenged, as the NNT value (see table) indicates a 50% decrease in pain, regardless of the initial intensity of pain. There is certainly a difference between reducing pain on a scale of 0–100 from 40 to 20, and from 90 to 45. The studies are primarily based on analgesia after third molar extraction and cannot be applied to a different type of severe postoperative pain. Although the intensity of pain after tooth extraction may be comparable to or higher than, for example, pain after hip replacement, the overall response of the organism is incomparable. Furthermore, it was revealed that Scott S. Reuben, author of many papers focusing primarily on the newer non-steroidal analgesics, falsified the results of the studies confirming their good effect. Therefore, in clinical practice, **procedure-specific analgesia** is increasingly used. This approach is based on the fact that the character and adverse effects of acute postoperative pain vary with the intensity of pain and that the treatment strategy should reflect that. The recommended procedure of the Czech Society of Anaesthesiology, Resuscitation and Intensive Care Medicine –Acute Postoperative Pain Management – is in line with this requirement and classifies the anticipated pain intensity into 3 degrees with a different analgesic regimen. The aim is to reduce the opioid requirement and thus minimize their adverse effects.

In general, a combination therapy is only meaningful if analgesics of various groups are used. Thus, it is possible to use a double or triple combination of non-opioid analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs – selective COX-2 inhibitors are most often mentioned in this context), and opioid analgesics. On the contrary, a combination of analgesics of the same group (especially various NSAIDs or opioid analgesics with different routes of administration, e.g. spinal and systemic – this does not apply to patients on long-term opioid therapy, see chapter 10) is not recommended, since there is no potentiation of analgesia, only of the adverse effects. This group of multimodal analgesia also includes the simultaneous administration of analgesics and adjuvants (see above). Most attention focuses on ketamine, which in low doses exhibits anti-hyperalgesic effect, potentiates opioid-induced analgesia and inhibits the development of tolerance to opioid analgesia. It may be administered only by anesthesiologists.

The last possible combination is the simultaneous administration of opioids and medications that inhibit some of their undesirable side effects on the gastrointestinal tract. These include alvimopan, which is not absorbed into the circulation after oral administration and only acts on the intestinal wall receptors, thus preventing the inhibition of gut motility induced by systemically administered opioids. Another specific peripherally-acting opioid receptor inhibitor (methylnatrexone) does not cross the blood-brain barrier after systemic administration and inhibits the effects of opioid analgesics on the intestines, as well as opioid-induced urinary retention.

Combination of locally administered medications

This group is represented mainly by centrally administered combination of opioid analgesics and local anesthetics in order to potentiate the analgesic effect of both, thereby reducing their dosage. Using lower concentrations of local anesthetics eliminates the risk of motor blockade, while the adverse effects of opioids remain largely unchanged. Find more details in the previous section.

Combination of systemically and locally administered medications

This mostly entails combining the local effect of local anesthetics and systemically administered analgesics. This combination will potentiate the analgesic effects of the local blockade, as well as eliminate discomfort in the area not affected by the blockade. Suitable medications for systemic analgesia include paracetamol, metamizole, or NSAIDs, particularly selective COX-2 inhibitors, especially if there is a concern about the risk of bleeding, such as in continuous neuraxial blockades.

Table 6.10 Oxford league table of analgesics (according to Bandolier, 2008)

Analgesic (mg)	Number of patients in comparison	Percent with at least 50% pain relief	NNT
Etoricoxib 180/240	248	77	1.5
Etoricoxib 120	500	70	1.6
Diclofenac 100	545	69	1.8
Celecoxib 400	298	52	2.1
Paracetamol 1000 + codeine 60	197	57	2.2
Aspirin 1200	279	61	2.4
Ibuprofen 400	5,456	55	2.5
Diclofenac 25	502	53	2.6
Piroxicam 20	280	63	2.7
Diclofenac 50	1,296	57	2.7
Ibuprofen 200	3,248	48	2.7
Pethidine 100 (IM)	364	54	2.9
Tramadol 150	561	48	2.9
Morphine 10 (IM)	946	50	2.9
Paracetamol 500	561	61	3.5
Celecoxib 200	805	40	3.5
Ibuprofen 100	495	36	3.7
Paracetamol 1000	2,759	46	3.8
Paracetamol 600/650 + codeine 60	1,123	42	4.2
Aspirin 600/650	5,061	38	4.4
Paracetamol 600/650	1,886	38	4.6
Ibuprofen 50	316	32	4.7

Analgesic (mg)	Number of patients in comparison	Percent with at least 50% pain relief	NNT
Tramadol 100	882	30	4.8
Tramadol 75	563	32	5.3
Aspirin 650 + codeine 30	598	25	5.3
Paracetamol 300 + codeine 30	379	26	5.7
Tramadol 50	770	19	8.3
Codeine 60	1,305	15	16.7
Placebo	> 10,000	18	N/A

Explanatory notes: The drugs are administered orally, unless stated otherwise (IM), NNT – number needed to treat, this value is obtained from randomized, double-blind studies and indicates the number of patients (compared with placebo) you need to treat to have at least 50% pain relief for at least 4–6 hours. **Note:** The lower the NNT value, the more effective the analgesic. If the NNT value is less than 2–3, it is considered a good analgesic by the authors of the table.

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6.5 Preemptive and preventive analgesia

In 1988, P. D. Wall published interesting data in the journal Pain suggesting that analgesia administered before the surgical incision, or amputation decreased postoperative pain, or the incidence of phantom pain, respectively, and reduced the need for postoperative analgesia. This was the first paper on preemptive analgesia. Preemptive analgesia was defined as measures preceding the surgical procedure, with the aim of preempting or alleviating postoperative pain by preventing central sensitization. Preemptive analgesia is of no use in patients who already suffered pain before surgery, as central sensitization has already developed.

In order to achieve successful preemptive analgesia, "complete analgesia" must be induced, which is:

1. deep enough to block all nociception
2. extensive enough to cover the entire operation area
3. long enough to last throughout the entire surgical procedure, as well as during the painful part of the postoperative period.

Many painful stimuli in the postoperative period may induce central sensitization (movements, coughing, dressing change, etc.). Careful postoperative pain management is therefore a key component of perioperative preemptive analgesia. To put it simply – the patient must be protected against postoperative pain. When using locoregional analgesia techniques, it is important to remember that the given area tends to have heterogeneous innervation, therefore it is advisable to combine locoregional analgesia with general analgesia.

Analgesia with nonsteroidal anti-inflammatory drugs (NSAIDs) is not deep enough to inhibit all nociception.

Subcutaneous wound infiltration with local anesthetics is not extensive enough.

Epidural analgesia alone may not cover the entire heterogenous innervation of the area. Furthermore, the site of the surgical trauma releases numerous substances, which pass into the circulation and act systemically.

In areas with multiple innervations, analgesia with a systemic opioid will reduce not only segmental, but also heterosegmental nociception. However, the use of high doses of systemic opioids is recommended, as postoperative sedation, constipation, urinary retention, and respiratory depression may result.

Ketamine in low analgesic doses has supraspinal analgesic effect, and acts as a spinal and supraspinal antihyperalgesic agent. Visceral pain mediated by the vagus nerve is transmitted to the medulla and triggers central sensitization. A combination of epidural analgesia acting segmentally and intravenous low-dose ketamine analgesia acting heterosegmentally is sufficient for preemptive analgesia and can avoid respiratory depression and protracted sedation. This combination needs to be applied before skin incision and finished only after surgery.

Achieving perfect preemptive analgesia is problematic for several reasons – pain is a multifactorial experience mediated by various substances, surgical pain is often heterosegmental, high-dose analgesia leads to the manifestation of its adverse effects. Moreover, the effectiveness of preemptive analgesia is difficult to measure, since many substances used during anesthesia have preemptive analgesic effect (e.g. nitrous oxide). Nevertheless, perioperative and postoperative analgesia should be conducted adequately, so that reasons for central sensitization during the procedure and in the postoperative period are kept to a minimum.

Therefore, the concept is broadening its scope and is currently referred to as **preventive analgesia**, which covers the entire period, in which perioperative pain occurs, with combination analgesic therapy using various routes of administration (see section 6.4).

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7

Recommendations for various types of surgical procedures in adults

7.1 Surgical procedures with anticipated mild postoperative pain

Mild postoperative pain is anticipated after arthroscopy, endoscopic urological procedures, minor gynecological procedures, superficial skin surgery, minor ENT procedures, etc.

7.1.1 Preoperative measures

There is no need for any special measures in the preoperative period. Premedication, if administered, should contain an analgesic component, which would extend its effect into the postoperative period. Instead of opioid analgesics, NSAIDs can be used, COX-2 selective inhibitors in particular, e.g. parecoxib 40 mg IV, IM, or oral meloxicam 15 mg, or naproxen 550 mg.

7.1.2 Intraoperative measures

The choice of anesthesia depends on the surgical procedure and on the patient's overall condition. Continuous locoregional anesthesia techniques are not recommended. About 15 minutes before the end of surgery, 1 g of IV paracetamol, or 1–2.5 g of metamizole in a short-term intravenous infusion can be administered. Paracetamol must be administered in an infusion over 10–15 minutes. Metamizole in an initial dose of up to 2.5 g should be administered in an infusion with at least 500 mL of a suitable carrier solution.

The surgeon may perform a local infiltration of the wound (ropivacaine 0.75%, or bupivacaine 0.5%) to improve the immediate postoperative patient comfort.

7.1.3 Postoperative measures

In the postoperative period, non-opioid analgesics are preferred, e.g. metamizole 1–2.5 g in 100-mL saline IV three times daily (up to 5 mg per day), or paracetamol 4 × 1 g IV (up to 4 g per day). If the pain is accompanied by inflammation or after tooth extraction,

NSAIDs are more effective. If the patient cannot take oral medication, it is possible to use a mixture of diclofenac 30 mg + orphenadrine 12 mg in saline IV every 12 hours, diclofenac alone – up to 75 mg in an infusion every 12 hours, or parecoxib 40 mg IV (IM) every 12 hours, especially if there is a risk of bleeding (ENT procedures, endoscopic urological procedures).

Oral medication should be started as soon as possible, e.g. a double combination of paracetamol 4 x 1 g + diclofenac 2 x 75 mg, naproxen up to 3 x 550 g, or ibuprofen 3 x 800 mg. Another option is to combine paracetamol 4 × 1 g + tramadol 50–100 mg, or if the pain is more intense, a triple combination of paracetamol + diclofenac (ibuprofen, naproxen) + tramadol.

If analgesia is insufficient, strong opioid analgesics may be administered, e.g. piritramide 15 mg SC, morphine 5–10 mg SC, or pethidine 50–100 mg SC.

7.1.4 Alternative options

Peripheral nerve blockade may be performed preoperatively before general anesthesia.

Intraoperatively, if general anesthesia is used, 20–25 mg of ketamine IV may be administered during surgery.

7.2 Surgical procedures with anticipated moderate postoperative pain

Moderate pain is anticipated after laparoscopic surgical procedures, videothoracoscopy, hernia repair, hysterectomy (vaginal), mastectomy, thyroidectomy, spinal disc surgery, etc.

7.2.1 Preoperative measures

Postoperative pain management may be influenced by appropriate premedication before surgery. Many health care facilities have a positive experience with preoperative administration of paracetamol (0.5–1 g rectally or orally). Rectally administered paracetamol is not absorbed in a standard way (see section 6.2.2) and up to 40 mg/kg may be required for good effect. Long-acting NSAID may be added as well (meloxicam 15 mg, duration of action – 24 hours). Contraindications, such as intolerance, drug allergy, or peptic ulcer disease, must be respected. NSAIDs are not recommended as premedication for surgical procedures with a higher risk of bleeding (certain ENT procedures, endoscopic urological procedures).

7.2.2 Intraoperative measures

The choice of anesthesia and anesthetics has a significant influence on postoperative pain. High-quality intraoperative analgesia is in the hands of an anesthesiologist who selects the most suitable opioid analgesic based on the type and duration of the surgical procedure (e.g. sufentanil, fentanyl, remifentanil, alfentanil) and its effect is potentiated by other anesthetics. About 15 minutes before the end of surgery, 1 g of IV paracetamol in a short-term intravenous infusion, or metamizole may be administered. Up to 2.5 g of metamizole in a 100-mL infusion of carrier solution may be administered, if it had not already been given before surgery. If that were the case, only 1 g of metamizole is administered.

If the surgical procedure is performed under locoregional anesthesia or a combination of locoregional and general anesthesia is used, thanks to the persisting locoregional anesthesia it is possible to improve the patient's postoperative comfort, enhance and prolong analgesia in the postoperative period and at the same time reduce the consumption of other analgesics. For example, 0.2 mg of preservative-free morphine added to a spinal blockade with bupivacaine results in a significant prolongation of high-quality postoperative analgesia with minimal increase in costs. Caution! Currently it is not possible to use commercial preparations of morphine for spinal administration, as they contain preservatives. However, many health care facilities solve this problem in cooperation with pharmacies, which can prepare a purified preparation of morphine.

The surgeon may perform a local infiltration of the wound (ropivacaine 0.75%, or bupivacaine 0.5%) to significantly, yet temporarily improve postoperative patient comfort.

7.2.3 Postoperative measures

Depending on the type of surgical procedure, a high-quality post-operative analgesia consists of a regular administration of non-opioid analgesics and weak opioid analgesics for 1–2 days after surgery. For example, paracetamol 1 g every 6 hours (IV, rectal or oral administration), or metamizole 1 g IV every 6 hours, or 2.5 g every 12 hours (maximum dose per day: 5 g), or in combination with tramadol up to a maximum dose per day of 400 mg (continuous administration in an infusion solution lasting 24 hours, or 50–100 mg boluses every 6 hours are recommended). Another option is to add NSAIDs, unless contraindicated. A suitable NSAID is e.g diclofenac, which can be added to an infusion with tramadol at a dose of 100–150 mg over 24 hours, or as a separate short-term IV infusion of 50–75 mg. Alternatively, 100 g of ketoprofen diluted in 20-mL saline may be used as an IV bolus. Another dose can be administered after 12 hours.

If analgesia is insufficient, tramadol may be replaced with a strong opioid analgesic (morphine 10 mg SC every 4–6 hours, piritramide 7.5–15 mg SC or IV every 8 hours). If there is an existing IV access, IV administration is preferred, in smaller increments.

If the patient still feels that the treatment of pain is not sufficient, it is necessary to perform an examination and evaluation of the patient to rule out that severe pain might indicate a complication of the surgery. Then we proceed as with surgical procedures with severe postoperative pain. It is important to remember that the perception of pain is highly individual.

As soon as the condition of the patient allows, it is advisable to switch to oral administration.

7.2.4 Alternative options

Ketamine

In several countries, ketamine is commonly used to treat postoperative pain (Austria, France). It has the advantage of a different mechanism of action (NMDA receptors), effect on neuropathic pain, and it does not cause respiratory depression. Unless contraindicated (hypertension, epilepsy, psychiatric disorders), ketamine can be used in a dose of 1 mg/kg in an infusion solution over 24 hours. If there is a higher risk of chronic postoperative pain (amputation of limbs, etc.), it is sometimes recommended to administer a bolus of 0.5 mg/kg of ketamine after the induction of anesthesia and then administer a continuous infusion with ketamine in the above-mentioned dosage.

7.3 Surgical procedures with anticipated severe postoperative pain

7.3.1 Introduction

This group includes surgical procedures, which require the use of high doses of opioid analgesics to treat acute postoperative pain, or systemic analgesia alone is no longer sufficient and it is necessary to combine systemic administration of analgesics with continuous locoregional analgesia techniques. Theoretically, even in severe postoperative pain, it is possible to use high doses of strong opioid analgesics that do not have a ceiling effect. However, this would result in a significant increase in complications, the most serious concern being ventilation (sedation, hypoventilation, atelectasis, hypercapnia, hypoxemia). Therefore, a combination with continuous locoregional analgesia techniques is preferable. Locoregional anesthesia or analgesia only affects the part of the body, which is the source of the pain, and allows us to significantly reduce the amount of systemically administered analgesics.

Severe postoperative pain is anticipated e.g. in bone surgery with extensive damage to the periosteum (total knee replacement, scoliosis surgery). While in total knee replacement a femoral nerve blockade in combination with general anesthesia is preferable, in scoliosis surgery the introduction of a continuous locoregional blockade is practically (and technically) impossible. A special group within this category includes thoracic procedures performed via thoracotomy. Respiratory movements provoke pain in the surgical wound, which is further aggravated by the chest tube irritating the pleura. This results in shallow breathing and impaired expectoration in the postoperative period. The postoperative use of opioid analgesics alone may lead to a vicious circle with the aforementioned complications. A similar problem occurs in surgery on the upper abdomen (resections of the stomach, pancreas, liver) and in procedures performed using a lumbotomy (nephrectomy) approach, in which the pathophysiology of pain is similar. In these surgical procedures, a properly functioning thoracic epidural analgesia is of major importance, especially in reducing postoperative complications related to ventilation.

7.3.2 Preoperative measures

In indicated cases, the anesthesiologist provides a suitable locoregional anesthesia after previously obtaining informed consent and educating the patient. A continuous epidural catheter must be placed at an appropriate level depending on the surgical procedure (e.g. in the thoracic region for procedures on the upper abdomen), and a test dose must be administered to rule out incorrect position of the catheter (spinal position).

The attitude towards continuous epidural blockade has been constantly re-evaluated. In the 1990s, thoracic epidural analgesia (TEA) was recommended over lumbar epidural analgesia in terms of improving the motility of the gastrointestinal tract, as well as improving cardiovascular stability. Thus, continuous TEA was used more commonly in the past and its indications were more liberal. More recently, possible complications are increasingly emphasized (mainly bleeding into the spinal canal with neurological consequences), and the indications for epidural techniques are becoming stricter. For example, in total knee replacement, epidural analgesia is no longer recommended as a routine technique and is replaced with femoral nerve blockade from the anterior approach, which has fewer severe complications. The influence of sym-

pathetic nerve blockade during epidural anesthesia on improved blood flow to the gastrointestinal tract has also been recently questioned. Several studies demonstrated a reduced blood flow to the intestinal wall associated with a decreased blood pressure during TEA. Despite all these concerns, TEA has an undeniable importance in surgical procedures with anticipated severe postoperative pain. It is still one of the methods of choice in thoracic surgical procedures and extensive surgical procedures on the upper abdomen. The issue of introducing a catheter to continuous nerve blockade in a patient under general anesthesia is often discussed. In Germany and Austria, it is strictly recommended to introduce epidural analgesia only in awake patients. The catheter is often inserted either the day before surgery, or in a reasonable amount of time before the procedure in the recovery room. In the UK, the blockade is often performed only after the induction of general anesthesia or under deep sedation. Nevertheless, even in the UK there is a growing trend of performing epidural puncture while the patient is awake in order to prevent accidental damage to the spinal cord or spinal root.

The administration of systemic analgesics (opioid analgesics in particular) in patients without pain in the preoperative period is not indicated.

7.3.3 Intraoperative measures

The scope of surgical procedures in this category mostly requires a balanced general anesthesia with strong opioid analgesics, or a combined anesthesia with a continuous locoregional technique.

Opioid analgesics used during general anesthesia often have a short-term effect and it is necessary to provide analgesia in the early postoperative period. After a major surgical procedure, the patient very often wakes up in the operating room with the doses of opioid analgesics reduced towards the end of the procedure in order to achieve optimal ventilation. In these cases, non-opioid analgesics should be administered before the end of surgery to produce a sufficient effect in combination with the reduced dosage of opioids. The administration of NSAIDs in the immediate perioperative period is not recommended due to a higher risk of bleeding complications. In adults, paracetamol or metamizole may be administered in a dose of 1 g IV in a short-term infusion (15 mg/kg). The first dose of metamizole may be up to 2.5 g in a 500-mL infusion. Continuous intraoperative administration of short-acting opioids (remifentanil, alfentanil) runs the risk of a very rapid onset of pain after the medication is discontinued, and it is therefore necessary to induce analgesia before the continuous infusion of short-acting opioids is stopped. To ensure a painless transport of the patient to a recovery room or intensive care unit, short-acting opioid analgesics may be used (50–100 mcg of fentanyl IV, titrate by 25 mcg, 5–15 mcg of sufentanil IV, titrate by 5 mcg). When a long-acting opioid (morphine, piritramide) is administered intravenously before the patient leaves the operating room, extra caution must be exercised to prevent maximum effect while transporting the patient with all the adverse effects (respiratory depression, hypotension). In some European countries, 0.1 mg/kg of IV piritramide is administered about 30 minutes before the end of surgery. If a continuous locoregional anesthesia technique has been introduced preoperatively, a combined anesthesia may follow with the administration of medication into the catheter from the very start of the surgical procedure, which would at the same time significantly reduce the requirement of systemically administered opioids. The issue of epidural administration of local anesthetics (LA) in combination with strong opioid analgesics, as opposed to local anesthetics alone, or an epidural administration of opioid analgesics alone is debatable. Similarly, there are no clear recommendations regarding the concentration of local anesthetics. Bupivacaine is clinically used in a wide range of concentrations – from 0.1 to 0.2%. If the patient develops severe hemodynamic instability (major blood loss), the catheter can be left *in situ* without administration and analgesia may be started only before the end of the surgical procedure. The administration should then start well in advance so that skin suture is already performed under locoregional analgesia (about 30–45 minutes before the end of the procedure).

The role of the surgeon in intraoperative pain management is no less important. Studies show that modifications of the standard surgical techniques may cause less postoperative pain. In total knee replacement, the introduction of drains is debated, as it leads to greater postoperative pain. Similarly, the advantages of anterior thoracotomy over posterolateral thoracotomy, intracostal sutures over pericostal sutures for closing a thoracotomy, or transverse laparotomy over longitudinal cut. However, the implementation of modified surgical procedures is at the discretion of the surgeon. Interestingly, the currently routine intraoperative use of shortwave diathermy causes less pain in the early postoperative period and results in lower analgesic requirement and less bleeding.

7.3.4 Postoperative measures

As already mentioned, in the postoperative period, analgesia is administered into the catheter for locoregional anesthesia, or is initiated as soon as possible. If the patient is experiencing discomfort, it can be combined with non-opioid analgesics (paracetamol or metamizole IV, orally up to a total dose of 4 g/24 h), or coxibs (parecoxib 2 x 40 mg IV, celecoxib 2x 100 mg orally) with the advantage of a minimal effect on blood clotting.

If continuous blockade is not introduced, it is usually necessary to administer strong opioid analgesics in the early postoperative period, either as an IV (titration) bolus (morphine 5–10 mg IV, piritramide 7.5–15 mg IV), or as a continuous IV infusion (sufentanil 15 mcg/h, piritramide starting with 1 mg/h). Continuous intravenous administration of strong opioid analgesics is one of the most effective and at the same time least safe techniques, with high demands on monitoring vital signs of the patient. In this respect, it is preferable to use patient-controlled analgesia (PCA). Within multimodal analgesia, a combination of opioid analgesics and non-opioid analgesics, coxibs, or NSAIDs is recommended (for dosage see above). If analgesia is insufficient, it is necessary to administer a bolus dose and increase the dose in the catheter if locoregional analgesia is used, or repeatedly administer a titration bolus of a strong opioid analgesic IV if systemic analgesia is used, until a satisfactory analgesia is achieved, or alternative techniques are used. Intramuscular administration of strong opioid analgesics is currently deemed obsolete, as the administration itself causes pain and can be replaced with other routes of administration (subcutaneous or fractionated intravenous administration, see above). The use of pethidine is not recommended due to its toxic metabolite (norpethidine).

7.3.5 Alternative options

Intraoperative use of ketamine can be considered an alternative technique. Several studies have shown a positive effect of subanesthetic doses of ketamine on reducing the requirement of strong opioids in the intraoperative and postoperative periods, in a variety of surgical procedures. However, there is still no evidence of the effect of

ketamine on long-term clinical results, and several studies have not demonstrated any effect of ketamine on the reduction of the adverse effects of opioid analgesics, even at lower doses. In certain types of surgical procedures, there is no data available on the transferability of the results from studies on other surgical procedures (e.g. total knee replacement). Based on these data, a routine administration of ketamine is not recommended for the individual surgical procedures. If ketamine is used, it is administered IV at low doses during surgery (0.25–0.5 mg/kg), which can be followed by a continuous administration of 0.125–0.25 mg/kg/h. Doses of ketamine under 0.15 mg/kg IV do not show any significant difference in opioid-sparing effect.

Based on the available data, incisional techniques, in which the surgeon infiltrates the surgical wound with local anesthetics before the incision, or rinses the wound with local anesthetics before closing it, or leaves a catheter in the wound for a continuous administration of local anesthetics cannot be currently considered routine techniques.

Patient-controlled analgesia (PCA) has the advantage of actively engaging the patient in postoperative pain management. Assessing the degree of pain is strictly individual, and the administration of analgesics by the patient significantly contributes to treatment optimization. This technique is relatively safe and can be used not only for intravenous administration of strong opioid analgesics, but also for the administration of local anesthetics in continuous peripheral nerve blockades (including epidural, PCEA). However, it is more demanding in terms of patient cooperation (postoperative level of consciousness), and especially in terms of equipment (PCA device). Many studies comparing locoregional analgesia techniques with a systemic administration of opioid analgesics administer opioids in the PCA mode. Basic information on patient-controlled analgesia is provided in section 6.2.1.

References

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8

Postoperative pain management in children

High-quality postoperative pain management is an essential prerequisite for a successful care of a pediatric patient after surgery. It aims to eliminate postoperative pain and thereby reduce perioperative stress of the child and minimize any negative memory traces, which may significantly affect communication with health professionals, hospital stay and any other surgical interventions that might follow.

It is important to remember that even very young children feel pain with the same intensity as adults.

8.1 Pathophysiology of pediatric pain

It has been demonstrated that peripheral receptors, pain pathways, and cortical centers for the perception of pain are formed and physiologically active already in the 24th gestational week. This implies that pathophysiological mechanisms of pain in infants are similar to those in adults. The following section summarizes the specific aspects of pediatric pain at various levels of pain perception.

A traumatic, inflammatory, or another type of painful stimulus results in the release of prostaglandins, bradykinin, etc. in the tissue. These substances activate nociceptors – specialized endings of sensory fibers of the peripheral nervous system, which are fully developed already in fetal life (polymodal nociceptors and mechanoreceptors). Slow-conducting unmyelinated thin C fibers (2 m/s) arise from polymodal nociceptors, whereas thin myelinated A-delta fibers arise from mechanoreceptors. C fibers carry slow, secondary, prolonged pain, while A-delta fibers convey primary, fast, localized pain.

These fibers carry pain impulses to dorsal horns of the spinal cord. Complex interactions occur in the dorsal horn between afferent neurons, interneurons and descending modulatory pathways that modulate the activity of second-order neurons of the spinothalamic tract. Information about pain is then carried to the thalamus and midbrain where it is processed and continues to a cortical center for pain perception

and interpretation. The histological structure of the dorsal horn of spinal cord in newborns, i.e. the localization of Rexed laminae, is very similar to that in adults. Its complete maturation happens around the 25th week of prenatal life. Thalamocortical tract is developed in the 29th week and from that moment pain is interpreted in a similar way as in adults.

The mechanisms of pain modulation are also functional already in childhood. These include descending inhibitory pathways terminating in dorsal horns of the spinal cord with serotonin and norepinephrine as neurotransmitters and suppressing pain through endorphins and enkephalins. The levels of these inhibitory neuropeptides are significantly lower after birth; thus, it is assumed that the level of pain in newborns is higher than in several months old children. The classic gate-control theory proposed by Melzack corresponds to the current knowledge of the general mechanism underlying pain perception in very young children.

8.2 Pharmacokinetics in children

Postoperative pain is an acute pain with rapid onset, which gradually resolves in most cases. Nevertheless, the child should not feel any pain after surgery, thus it is necessary to prevent postoperative pain, and not wait until the first symptoms appear to start treatment. This can be achieved by a carefully considered administration of analgesics and sedatives and their proper dose. The following section summarizes different pharmacokinetics in children compared to adults.

The *absorption* of medications is lower in newborns than in infants and adults. In the case of oral administration, it is due to a significantly lower acidity of gastric juice and immaturity of neonatal gastric mucosa; in the case of intramuscular administration, it is caused by a high water content in muscles, vasomotor instability and possible centralization of blood flow.

The *distribution* of medications in the neonatal period is accelerated by hyperkinetic circulation and shorter circulation time. Another very important factor is reduced plasma protein binding, which leads to higher levels of free circulating medicine. Albumin concentration is 35 g/L (45 g/L in adults) and in addition, fetal albumin has lower affinity to drugs. Increased bilirubin can also displace the drug from its binding site and thus increase its free fraction even more. On the other hand, higher body water content in newborns (70–75% compared to 55–60% in adults) increases the distribution volume for water soluble medications and thus reduces their concentration with the dose remaining basically the same.

Immature blood-brain barrier allows the penetration of a higher amount of drugs to the brain and their accumulation. This applies particularly to barbiturates and opioid analgesics.

The *elimination* in newborns depends primarily on the maturity of liver and kidneys. The immaturity of the liver slows down enzymatic processes that degrade some drugs and thus prolongs their half-life. The maturation of the detoxification ability of the liver is variable, it takes weeks or months depending on the individual functions.

Due to the lower renal perfusion in the immediate postnatal period, glomerular filtration, as well as tubular secretion and reabsorption are reduced. Renal excretion of drugs or their metabolites is slower and it is therefore necessary to reduce the dose and prolong the dosing interval of many drugs. Renal functions are mature at about 6 months of age.

8.2.1 Administration of perioperative analgesia in children

The most commonly used route of administration for analgesics in pediatric perioperative and prehospital emergency care is intravenous administration, either via peripheral venous cannula or via central venous catheter. It is considered the most reliable route of administration in terms of the amount of the active ingredient that is administered. Intramuscular or subcutaneous routes of administration are affected by the centralization of blood flow, which may modify their effect. The amount of the active ingredient administered orally, rectally, or nasally may be uncertain. It depends on the child's willingness to cooperate and on the skills of the medical personnel. Nevertheless, these routes of administration are also frequently used.

Epidural administration in perioperative analgesia is described below.

8.3 Systemic analgesics in pediatric perioperative care

Opioids are the most effective analgesics in pediatric care. Nevertheless, long-term administration of opioid analgesics is associated with concerns about their adverse effects, respiratory depression in particular, which often leads to underdosing. Indeed, their effect is prolonged in very young children, and their adverse effects are more pronounced, since they penetrate the blood-brain barrier more easily and opioid receptors are also more sensitive in children.

Strong opioid analgesics can only be safely administered to young children postoperatively, provided that any potential complications that might arise can be solved, including the possible use of artificial ventilation. Administration of opioids requires a constant monitoring of vital signs.

The often-discussed physical dependence to opioid analgesics, accompanied by withdrawal symptoms upon their discontinuation, develops but with large interindividual differences. Especially in younger children, e.g. infants and babies, dramatic symptoms of withdrawal syndrome may be observed already after several tens of hours of administration, if high doses of opioid analgesics were used.

Opioid administration must then be usually restored and the dose is reduced more slowly.

Morphine is the most widely used opioid analgesic in this group for the treatment of pediatric postoperative pain. It is used in premedication and especially in postoperative pain management, usually in the form of continuous administration. Due to the slow onset of action if continuous administration is used, either a "rescue" dose of a non-opioid analgesic is administered, or the administration of morphine is already started during surgery. Effective doses (Table 8.1) provide analgesia and release of tension and anxiety without substantially affecting consciousness. Higher doses cause nausea, vomiting, pruritus, and spasms, which may be observed in newborns even at regular doses. The hemodynamic effect of morphine is minimal, but by reducing the sensitivity of the respiratory centers in the brainstem to hypoxia and hypercapnia it may lead to significant respiratory depression. Bradypnoea is caused by the inhibition of the respective centers in the medulla oblongata. Morphine also suppresses the cough reflex, decreases the gastrointestinal motility, increases the tone of the sphincter of Oddi, urinary bladder, and ureters.

Fentanyl and fentanyl derivatives are more commonly used during anesthesia and in continuous analgesic sedation in intensive care, when artificial ventilation is used,

rather than in standard postoperative care. They are significantly more potent than morphine (sufentanil 1000 times) and there is a great inter-individual variability. They are highly lipophilic, and easily cross the blood-brain barrier, resulting in a fast onset of action. Since they are soon redistributed into tissues, the duration of their effect is relatively short. However, with repeated administration their plasma levels decrease more slowly and the effect is prolonged. In young children that have lower levels of plasma proteins, the duration of action is difficult to predict.

After the administration of fentanyl derivatives, hemodynamics remains stable, but there is a significant respiratory depression, which starts very quickly upon IV administration. The rigidity of the chest wall induced by these medications further exacerbates breathing difficulties.

Currently, only sufentanil is commonly used in pediatric care. In addition to its excellent analgesic potency, it has a marked sedative-hypnotic effect and causes milder respiratory depression than fentanyl at comparable analgesic doses.

Given the recommendation not to administer strong opioid analgesics in boluses, there has been a significant decline in the use of *piritramide* and *pethidine*. Moreover, pethidine causes nausea, vomiting, bronchospasm, and has demonstrated a negative inotropic effect.

More recently, there has been a revival in the use of *nalbuphine* as a perioperative analgesic (i.e. during surgery and in postoperative care). A mixed agonist at the κ-receptors, *nalbuphine* does not cause respiratory depression or addiction, and as an antagonist at the μ-opioid receptors it antagonizes respiratory depression caused by other opioids. For the same reason, however, it should not be used with other opioids. Nalbuphine is used in perioperative pain management for minor surgical procedures and in postoperative analgesia for moderate pain.

Naloxone is a widely used opioid antagonist. In a dose titrated up to 10 mcg/kg IV or IM, naloxone antagonizes not only the respiratory depression, sedation and most adverse effects of opioids, but also analgesia. The half-life of its effect is relatively short (40–60 minutes), hence there is a risk of respiratory depression re-occurring. Furthermore, a rapid IV opioid antagonization may result in circulatory instability with an increased blood pressure and heart rate, and confusion of the child. The administration of naloxone is certainly not a standard way to terminate anesthesia, but a means of reversing opioid overdose.

Tramadol is a moderately effective analgesic in pediatric care, which is still widely used. It has less marked hypnotic and sedative effects compared to strong opioid analgesics and low potential for addiction. Tramadol does not induce respiratory depression, but it often causes nausea and vomiting in children. It has the advantage of good effect after oral, rectal, and parenteral administration. The indication for tramadol is postoperative pain management after surgical procedures with mild to moderate pain.

Codeine is contraindicated in children due to the risk of respiratory depression in a subset of population with ultra-rapid metabolism of codeine to morphine. Recently, FDA issued warning that tramadol should not be used to treat pain in all children younger than 12 years and in children younger than 18 years after the removal of tonsils and/or adenoids. No such warning was given by the European Medicines Agency and other authorities.

Table 8.1 Doses of opioid analgesics in pediatric perioperative pain management. Doses that do not affect spontaneous breathing activity are in bold.

	Single dose	Continuous administration
morphine	0.05–***0.2*** mg/kg IM, IV	0.01–0.02 mg/kg/h ***0.5***–1 mg/kg/24h
fentanyl	***1***–4 mcg/kg IM, IV	***1***–2 mcg/kg/h
sufentanil	***0.1***–0.5 mcg/kg IM, IV	***0.2***–1 mcg/kg/h
pethidine (meperidine)	***1*** mg/kg IM, IV	
piritramide	***0.05–0.2*** mg/kg IM, SC; ***0.05–0.1*** mg/kg IV	
nalbuphine	***100–250*** mcg/kg	
tramadol	***1–1.5*** mg/kg IV, IM, PO, PR.	***0.25*** mg/kg/h

Ketamine is an intravenous dissociative anesthetic, which is usually used in combination with benzodiazepines to suppress its hallucinogenic effects. It is particularly indicated for anesthesia for procedures on the body surface – dressing changes, treatment of burns, plastic surgery, etc. (the usual dose for inducing general anesthesia is 2–5 mg/kg IV according to the age of the child). In subanesthetic doses of up to 1 mg/kg IV, ketamine is an excellent analgesic with a rapid onset of action, without psychotomimetic effects, but with a relatively short action (10–20 minutes). The same result is achieved by administering 2–3 mg/kg of ketamine IM or PR. It is indicated for analgesia in prehospital care and as an analgesic component of balanced anesthesia. For anesthesia in patients with unstable circulation, it is a safer alternative to inhalational anesthetic sevoflurane.

Non-opioid analgesics are widely used in postoperative pain management in children, particularly in recent years, when their intravenous forms have become commonly available. They act mainly on peripheral receptors in the damaged tissue, but they also have a central effect. In general, their analgesic effect is weaker than the effect of opioids, they can be used in combination with opioid analgesics, or in the treatment of mild postoperative pain. In pediatric pain management, the most commonly used analgesics in this group are paracetamol, metamizole, and ibuprofen.

Paracetamol is the most widely used non-opioid analgesic. Intraoperatively, it is administered intravenously as a supplement to general anesthesia. In postoperative care, paracetamol is used in intravenous and rectal forms already in newborns. A therapeutically effective (especially antipyretic) plasma concentration is 20 mcg/mL, maximum allowable plasma concentration is 120 mcg/mL. Severe hepatotoxic complications were reported at concentrations greater than 300 mcg/mL. Paracetamol dose is shown in Table 8.2. While in oral and rectal administration the initial dose must be increased to 40 mg/kg, in IV administration this is not necessary due to the rapid increase in plasma concentration.

Metamizole is an analgesic with approximately the same analgesic effect as paracetamol. Similarly to paracetamol, metamizole has analgesic and antipyretic effects, and furthermore a spasmolytic effect. It is registered for use in children over the age of 3 months. IV administration is used most commonly, however, there is a risk of bronchospasm if administered rapidly. By contrast, the often-mentioned agranulocytosis is rather a theoretical complication.

Ibuprofen is used as a supplementary analgesic in oral and rectal forms, its administration is recommended in children over the age of 3 months (weighing more than 6 kg). It is contraindicated if there is a suspected bleeding from peptic ulcers and the gastrointestinal tract. IV form is available in some countries.

Diclofenac and indomethacin are only rarely indicated in pediatric postoperative pain management, selective COX-2 inhibitors are not widely used.

Table 8.2 Doses of non-opioid analgesics and sedatives in children

paracetamol	7.5–15 mg/kg IV; 15–20 mg/kg PR, max. 60 mg/kg
metamizole	15 mg/kg, max. 4 times daily
ketamine	1 mg/kg IV, 2–3 mg/kg IM, PR
ibuprofen	20 mg/kg in 3–4 doses PO, PR
diazepam	0.1–0.3 mg/kg IV, IM; 0.2–0.5 mg/kg PR
midazolam	0.025–0.1 mg/kg IV; 0.2–0.5 mg/kg PO, max. 10 mg 0.05–0.1 mg/kg/h cont.inf.
chloral hydrate	20–100 mg/kg PO, PR
promethazine	0.5–1 mg/kg IV, IM
chlorpromazine	0.5–1 mg/kg IV

8.4 Locoregional anesthesia and analgesia

Locoregional anesthesia techniques are increasingly used in pediatric anesthesia and analgesia. This is undoubtedly due to the availability of ever more sophisticated materials enabling both a single-injection and more importantly a continuous form of blockades and the availability of safer drugs. Nevertheless, the administration of locoregional anesthesia techniques in young children requires a good knowledge of these techniques, with respect to the anatomical, physiological and pharmacokinetic and pharmacodynamic differences in children. All regional anesthesia techniques in children are performed under general anesthesia, either inhalational, or intravenous, to avoid stress response and unexpected movements during the puncture, which may cause damage to the patient. However, this also eliminates the possibility to communicate with the child and get a basic idea if the puncture or catheter placement was successful. Locoregional anesthesia significantly reduces the analgesic requirements in the intraoperative and postoperative periods. A significant reduction in the consumption of opioid analgesics or their complete withdrawal is particularly appreciated. Always keep in mind that locoregional anesthesia using local anesthetics does not have a sedative component. Therefore, restlessness and crying in the postoperative period might not be caused by insufficient analgesia, but rather by a feeling of discomfort of the child.

8.4.1 Anatomical and physiological differences in children in relation to locoregional anesthesia

Young children have different anatomy compared to adults and it undergoes significant changes with age. Children have a relatively large head (one third of the body height in newborns), lower limbs are comparatively smaller, and an epidural or intrathecal administration of local anesthetics results in only a minimal decrease in blood pressure. The technique of locoregional anesthesia in young children is also influenced by the following factors:

- dural sac extends to S4 (S1 by the end of the first year)
- spinal cord reaches L4 (L1 by the end of the first year)
- intercristal line intersects the spine at L5–S1
- lumbar lordosis is not present
- epidural space contains very thin adipose tissue, which facilitates the spread of the local anesthetic and the penetration of the catheter
- plasma levels of albumin and alpha-1 glycoprotein are low, thus there is a lower binding capacity for local anesthetics and their unbound (free) fraction is higher
- sympathetic nerve blockade is minimal, the autonomic nervous system has a very little influence on the capillary and venous bed
- orientation when the needle penetrates tissues is difficult, as the structures exert less resistance

Local anesthetics (LA) act by slowing down the depolarization of nerve cells, preventing them from reaching the threshold potential, necessary for the initiation and propagation of the action potential. The penetration of LA into the nerve fiber is easier in thinly myelinated A-delta and C fibers carrying nociceptive signals, whereas thickly myelinated motor fibers are much more resistant. However, the immature, only thinly myelinated motor fibers in young children compared to adults might be affected by the anesthesia as well, resulting in a motor blockade.

Ester LA are metabolized quite rapidly by plasma cholinesterase, thus its low level in newborns prolongs their effect. Amide LA are metabolized in the liver at a significantly slower rate, resulting in a longer action, as well as duration of their toxic effects. This is observed especially in newborns, as they have a reduced detoxification ability of the liver and the already mentioned lower binding capacity of plasma proteins.

Currently, in the group of local anesthetics, lidocaine or trimecaine are used for infiltration anesthesia, and bupivacaine, levobupivacaine, and ropivacaine are used for nerve blockades.

8.4.2 Toxic reaction

There are feared toxic complications in pediatric locoregional anesthesia. They occur when a wrongly calculated, too high single or continuous dose is administered, or when local anesthetics are accidentally administered into the intravascular or intraosseous space. These complications present as cardiotoxic reactions (tachycardia, ventricular arrhythmias, myocardial depression, or cardiac arrest), or neurotoxic complications (seizures). If the child is conscious, there are warning signs preceding seizures, such as impaired speech, tinnitus, paresthesia, agitation, or somnolence. While a cardiotoxic reaction is very rare, seizures and disorders of consciousness can be witnessed mainly when a continuous dose of local anesthetics in postoperative care has not been calculated correctly. Neurotoxic complications are treated with oxygen inhalation, midazolam 0.2 mg/kg IV, or diazepam 0.2 mg/kg up to a maximum dose per day of 1 mg/kg as an anticonvulsant, or with muscle relaxation, tracheal intubation, and artificial ventilation. If circulatory complications develop, oxygen is the method of choice. If bradycardia and cardiac arrest occur, cardiopulmonary resuscitation is initiated, with the administration of inotropic agents (epinephrine, dopamine, atro-

pine), bicarbonate, and calcium. If ventricular fibrillation develops, defibrillation using 2–4 J/kg is performed. Anticonvulsants are also administered. Intralipid 20% significantly reduces plasma levels of local anesthetics. After a single dose of 2–5 mL/kg, Intralipid 20% is administered at 15 mL/kg/h according to the clinical signs of the patient.

8.4.3 Allergic reaction to a local anesthetic

Very rarely, an allergic reaction to a local anesthetic develops. Allergy, which is often stated in the documentation of the child, may be a reaction to the additives to local anesthetics, toxic reaction, collapse in connection with outpatient wound care, etc. Nevertheless, a different technique for the administration of anesthesia should be considered, and if needed, be fully equipped for dealing with an anaphylactic reaction.

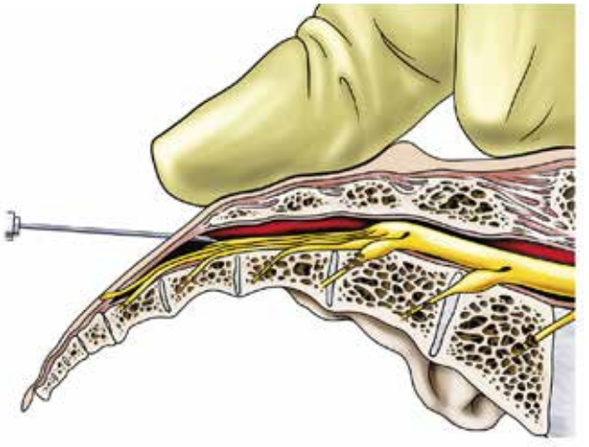
Locoregional anesthesia in children is performed in the following ways.

8.4.4 Epidural anesthesia

Epidural anesthesia is the most commonly used locoregional anesthesia technique in children. It uses the rapid spread of local anesthetics through the loose connective tissue in the space between the bone of the spinal canal and the dura mater. The anesthetic penetrates to spinal nerve roots and induces anesthesia in the area innervated by these roots. According to the level, it may be divided into caudal, lumbar, thoracic, and cervical blockades.

- A caudal blockade is performed by administering a local anesthetic into the epidural space through the sacral hiatus (Fig. 8.1). The dose of the local anesthetic is calculated based on age and weight and it induces anesthesia extending from the fundus of the urinary bladder, groin and perineum to the lower limbs. It is used for surgical procedures in these areas, especially in young children and newborns. In older children, sacral hiatus is less accessible for puncture.
- A lumbar approach is used in patients from toddler age. The puncture is performed at L3–L5 level, and the anesthesia extends to the level of the diaphragm. This type of anesthesia is suitable for orthopedic, urological, and abdominal surgery.
- A thoracic blockade is technically challenging due to the different shape of thoracic vertebrae. However, it is still widely used for anesthesia, and especially for postoperative analgesia in patients undergoing thoracotomy or chest wall reconstruction.
- A cervical epidural blockade is not used in pediatric anesthesia.

Local anesthetics may be administered either as a single dose (the effect lasts for about 4 hours), or continuously through a catheter placed into the epidural space (remains in place for 1–5 days). In postoperative pain management, local anesthetics may be combined with opioid analgesics (sufentanil, preservative-free morphine). In the first days after surgery, children with epidural analgesia must be sedated. Contraindications for epidural puncture include spinal defects, skin lesions at the injection site, and allergy to the local anesthetic. Most common complications are paresthesia due to the catheter irritating the spinal root, an accidental puncture of the dural sac with CSF leakage, and occasionally inflammatory complications.



Caudal epidural blockade – the most common form of regional anesthesia in children. The needle penetrates through the sacrococcygeal membrane into the sacral hiatus and into the epidural space. Cauda equina is infiltrated with local anesthetic.

Fig. 8.1 Caudal epidural blockade

8.4.5 Spinal anesthesia

An intrathecal administration of local anesthetics induces a sensory and motor blockade in the affected spinal segments. It is performed using a thin 27G spinal needle or smaller. CSF dripping from the hub of the spinal needle confirms that the needle is correctly placed. Despite its relative simplicity, spinal anesthesia is only rarely used in children, out of fear of post-dural puncture headache, postural hypotension, and surprisingly short (60–90 minutes) duration of anesthesia, which is not enough to provide postoperative analgesia.

8.4.6 Peripheral nerve blockades

Nerve blockades involve the infiltration of tissues in the immediate vicinity of peripheral nerve trunks with local anesthetics. The anesthetic blocks the nerve and causes numbness in the innervated area. For instance, a brachial plexus blockade is performed for surgery on the upper limb, an intercostal blockade for thoracotomy in older children, an ilioinguinal/iliohypogastric nerve blockade for hernia repairs, and a penile blockade for circumcision. Peripheral nerve blockades in children should be performed under general anesthesia. With the development of ultrasound-guided administration, these methods have been used with increasing frequency.

8.5 Perioperative pain management in children

The knowledge of the extent of the surgical procedure and the anticipated level of pain is essential for good perioperative pain management. It is necessary to consider it carefully and plan analgesia accordingly so as to meet the basic premise: a good balance of preoperative analgesia (i.e. premedication), intraoperative, and postoperative analgesia. With the right combination of drugs at these stages and proper timing of their

administration, postoperative analgesia may be performed in a significantly safer and more efficient way. In an optimal situation, premedication, anesthesia, and postoperative analgesia should be performed by the same physician.

An integral part of preoperative preparation is an interview with the parents and with the child (in a sensitive way, tailored to the child's age). They are assured that postoperative pain is common, that its intensity decreases with time and may fluctuate during the day and night, and most importantly, that the treatment of perioperative pain is possible and will be given full attention.

Intraoperative analgesia depends on the selected method of general anesthesia. It is essential to make sure that sufficient analgesia is provided for the period after recovery from anesthesia, for the transfer of the patient to the recovery room and for the initial phase of the patient's stay. Preventing a period without analgesia is very important and often underestimated. It can be bridged by starting a continuous administration of analgesics already during the last phase of the surgical procedure, or by a careful administration of a "rescue" bolus dose of an analgesic.

In addition to the pharmacological treatment of pain, it is very important to optimize environmental factors in the postoperative period. These negative effects include lack of privacy and constant noise on the postoperative ward, insensitive and unnecessary handling of the patient, and intense light. In certain situations, the presence of agitated parents at the bedside after the child arrives from the operating room may be questionable.

In the postoperative period, it is very important to distinguish an inadequately treated postoperative pain from distress and annoyance of the bedridden child. Both present as restlessness, crying, tachycardia, hypertension, avoidance of contact, and eating disorder. Lack of proper recognition may lead to an unnecessary increase in the dose of analgesics instead of using sedatives to supplement analgesia.

8.6 Monitoring the quality of postoperative pain management

Monitoring the level of postoperative analgesia and sedation is necessary, as different patients may respond to standard doses in a different way. A record of postoperative pain management, its monitoring and assessment has become a closely observed mandatory part of nursing documentation.

In children less than one year old, the most widely used scale is NIPS (Neonatal/Infant Pain Scale) evaluating the alterations of common activities of daily living of the child – crying, breathing, consciousness, limb movement, etc. ATTIA and POPSI are compiled in a very similar manner. In older infants and toddlers, the FLACC (Face-Legs-Activity-Cry-Consolability) scale proved to be most useful.

In children that can differentiate between images (from about the age of 4), VAS (visual analogue scale) may be used to evaluate the quality of postoperative analgesia. However, it is debatable whether children associate the color or pictorial symbols with a feeling of acute pain, or rather a feeling of discomfort or homesickness. The level of sedation may be determined using the relatively complex and comprehensive Comfort score.

In addition to the results of the assessment, an attentive care of an experienced nursing team plays a vital role in successful pain management.

Visual analogue scale for pain assessment in children

0 – no pain, 2 – mild pain, 4 – moderate pain, 6 – severe pain, 8 – very severe pain, 10 – worst possible pain

Neonatal/Infant Pain Scale (NIPS) for children less than 1 year old

Facial Expression		
0	Relaxed muscles	Restful face, neutral expression
1	Grimace	Tight facial muscles; furrowed brow, chin, jaw, (negative facial expression – nose, mouth and brow)
Cry		
0	No cry	Quiet, not crying
1	Whimper	Mild moaning, intermittent
2	Vigorous cry	Loud scream; rising, shrill, continuous (Note: Silent cry may be scored if baby is intubated as evidenced by obvious mouth and facial movement.)
Breathing Patterns		
0	Relaxed	Usual pattern for this infant
1	Change in breathing	Indrawing, irregular, faster than usual; gagging; breath holding
Arms		
0	Relaxed/Restrained	No muscular rigidity; occasional random movement of arms
1	Flexed/Extended	Tense, straight arms; rigid and/or rapid extension, flexion
Legs		
0	Relaxed/Restrained	No muscular rigidity; occasional random leg movement
1	Flexed/Extended	Tense, straight legs; rigid and/or rapid extension, flexion
State of Arousal		
0	Sleeping/Awake	Quiet, peaceful sleeping or alert random leg movement
1	Fussy	Alert, restless, and thrashing

A score greater than 3 indicates pain.

FLACC: a behavioral scale for scoring postoperative pain in young children

Categories	Scoring		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown; withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs; frequent complaints
Consolability	Content, relaxed	Reassuring by occasional touching, hugging, or being talked to; distractible	Difficult to console or comfort

FLACC score greater than 3 – consider an intervention. A score greater than 5 – it is necessary to increase analgesia.

Postoperative Pain Score (POPS) for infants

Indicator	0 points	1 point	2 points
Sleep during the preceding hour	none	brief period of 5–10 min	longer period – more than 10 min
Facial expression of pain	intense, all the time	less pronounced, intermittent	relaxed, calm
Quality of cry	piercing, high-pitched, painful	modulated, stops crying when we talk	does not cry
Consolability	none after 2 min	calms down after 1 min of consolation	calms down within 1 min
Sociability – eye contact, smile, interest, response	none	difficult to elicit	easily, for a long time
Sucking	none, in an uncoordinated way	3–4× and starts crying	vigorously, rhythmically, calms down
Spontaneous excitability	tremor, jerky movements	increased excitability	normal
Spontaneous motor activity	thrashing, constantly restless	mild restlessness	normal
Flexion of fingers and toes	constant, intense	less pronounced	none
Tone	greatly increased	slightly increased	normal

A score of 0 indicates maximum pain, 20 indicates no pain.

Comprehensive scale for the assessment of pharmacological sedation in ventilated children used at the Motol University Hospital in Prague

Alertness	deeply asleep	1
	lightly asleep	2
	drowsy	3
	fully awake and alert	4
	hyper-alert	5
Calmness/anxiety	calm	1
	slightly anxious	2
	anxious	3
	very anxious	4
	panicky	5
Respiratory response	no coughing and no spontaneous respiration	1
	spontaneous respiration with little or no response to ventilation	2
	occasional cough or resistance to ventilator	3
	actively breathes against ventilator or coughs regularly	4
	fights ventilator; coughing or choking	5
Physical movements	no movement	1
	occasional, slight movement	2
	frequent, slight movements	3
	vigorous movement limited to extremities	4
	vigorous movements including torso and head	5
Blood pressure	below baseline	1
	consistently at baseline	2
	infrequent elevations of 15% (1–3×/h)	3
	frequent elevations of 15% or more	4
	sustained elevations of 15% or more	5
Heart rate	below baseline	1
	consistently at baseline	2
	infrequent elevations of 15% (1–3×/h)	3
	frequent elevations of 15% or more	4
	sustained elevations of 15% or more	5
Muscle tone	relaxed, no muscle tone	1
	reduced muscle tone	2
	normal muscle tone	3
	increased muscle tone and flexion of fingers and toes	4
	muscle rigidity and flexion of fingers and toes	5

Facial expression	totally relaxed	1
	normal tone	2
	tension evident in some facial muscles	3
	tension evident throughout facial muscles	4
	facial muscles contorted and grimacing	5
Total points		

Target value: 15–27 points, Over-sedated: 14 points and less, Under-sedated: 28 points and more

Fig 8.2 Various scales and methods for measurement of pain intensity in babies and children

8.7 Recommendations for various types of surgical procedures in children

The following section offers recommendations for postoperative pain management in children. In each group of surgical procedures, the most suitable type of analgesia is presented, and several alternative options are provided.

8.7.1 Minor surgical procedures

(hernia repair, orchidopexy, appendectomy, minor orthopedic procedures, dental surgery, etc.)

Preoperatively: premedication with a marked sedative component – midazolam 0.2 mg/kg PO

Intraoperatively: general anesthesia as usual (usually inhalational), after the induction of anesthesia: sufentanil 0.1 mcg/kg and paracetamol 7.5–15 mg/kg IV or metamizole 10–15 mg/kg IV or nalbuphine 0.15 mg/kg

Postoperatively: paracetamol 15–20 mg/kg PR 4 times daily or ibuprofen 4–10 mg/kg PR 4 times daily

Alternative options

Preoperatively: premedication with a marked analgesic component – morphine 0.2 mg/kg IM (in children weighing more than 5 kg)

Intraoperatively: general anesthesia combined with an epidural blockade – levobupivacaine up to a max. dose of 2 mg/kg caudally, or ketamine 1 mg/kg IV.

Postoperatively: epidural blockade, metamizole can be added in a dose of 10–15 mg/kg IV, paracetamol 7.5–15 mg/kg IV, tramadol 1–2 mg/kg PR, PO 4 times daily (max. daily dose: 8 mg/kg or 400 mg)

8.7.2 Intermediate surgical procedures

(pyloroplasty, pyeloplasty, pediatric urology, thoracoscopy, laparoscopy, orthopedic correction, tonsillectomy, plastic surgery, etc.)

Preoperatively: premedication as usual, either midazolam 0.2–0.3 mg/kg PO or morphine 0.2 mg/kg IM. Given the need for strong intraoperative analgesia and a longer duration of the surgical procedure, an analgesic component of premedication is not necessary for postoperative analgesia

Intraoperatively: balanced anesthesia, analgesia: sufentanil 0.2–0.5 mcg/kg, or a continuous administration of 0.3–1 mcg/kg/h, or fentanyl 0.5–1 mcg/kg/h

Postoperatively: metamizole 10–15 mg/kg IV 3 times daily, or paracetamol 7.5–15 mg/kg IV 4 times daily, or tramadol 1–2 mg/kg IV 4 times daily, or nalbuphine 0.1–0.2 mg/kg up to 4 times daily. If this is not sufficient, then continuous administration of morphine 15–30 mcg/kg/h (5–10 mcg/kg/h in newborns)

Alternative options

Intraoperatively: combined anesthesia with an epidural catheter placed at an appropriate level, a bolus dose of bupivacaine, or levobupivacaine at a maximum dose of 2 mg/kg. During the procedure, start a continuous administration of levobupivacaine, or bupivacaine 0.2 mg/kg/h in children weighing less than 10 kg, or 0.3 mg/kg/h in children weighing more than 10 kg.

Postoperatively: continue with the continuous administration into the epidural catheter. If this is not sufficient, you can add metamizole 10–15 mg/kg IV, paracetamol 7.5–15 mg/kg IV, or tramadol 1–2 mg/kg IV, the dose may be repeated (see above)

8.7.3 Major surgical procedures

(thoracotomy, extensive surgical revision of the abdominal cavity, scoliosis surgery, major orthopedic surgery, neurosurgical remodeling, corrective dental surgery, etc.)

Preoperatively: the same as with intermediate surgical procedures

Intraoperatively: balanced anesthesia, the same as with intermediate surgical procedures. Before the end of surgery, it is possible to start a continuous administration of morphine 15–30 mcg/kg/h (5–10 mcg/kg/h in newborns), or sufentanil 0.2–0.3 mcg/kg/h and thereby avoid a period without proper analgesia when transferring the patient to a postoperative ward.

Postoperatively: continuous administration of morphine 15–30 mcg/kg/h (5–10 mcg/kg/h in newborns), or sufentanil 0.2–0.3 mcg/kg/h. If continuous opioid analgesia is not sufficient, it is possible to add metamizole 10–15 mg/kg IV 3 times daily, or paracetamol 7.5–15 mg/kg IV 4 times daily.

Alternative options

The same as with intermediate surgical procedures.

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9

Postoperative pain management during pregnancy, after cesarean section, and during breast-feeding

9.1. Analgesia during pregnancy

A critical period in pregnancy covers the first trimester with respect to potential teratogenicity and the third trimester with respect to the influence on the newborn, or the premature closure of the ductus arteriosus (ductus Botalli).

Paracetamol is generally considered a safe analgesic throughout pregnancy.

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the synthesis of certain prostaglandins and thus may have some adverse effects, especially in the second half of pregnancy. Although the results of clinical trials are not conclusive, NSAIDs are not recommended in women planning to conceive and during the first trimester, as they may increase the risk of miscarriage according to several studies. NSAIDs are contraindicated in the last 2–3 months before the expected delivery date due to the risk of premature closure of the ductus arteriosus and pulmonary hypertension in the newborn.

Codeine and **tramadol** are weak opioid analgesics commonly used for postoperative analgesia. They are not recommended shortly before delivery due to the risk of respiratory depression in the newborn, and a prolonged use in the prenatal period might incur the risk of withdrawal syndrome in the newborn. Furthermore, tramadol is not recommended due to the lack of data on its use in pregnant women.

Morphine is safe in terms of potential teratogenicity. With regard to its use, the same applies as with codeine.

9.2 Analgesia after cesarean section and during breast-feeding

Many drugs used in postoperative pain management are transferred to breast milk to a greater or lesser extent, and thus affect the infant as well. The most commonly performed surgery in lactating women is a cesarean section. In addition, breastfeeding women may need to undergo various surgical procedures that may cause severe pain. Therefore, it is essential to provide adequate analgesia. The analgesic regimen should be both effective and safe, with minimal side effects that would trouble the woman to such an extent that she would not be able to breastfeed and take care of her baby, or that would have adverse effects on the infant. Currently, there is no gold standard for postoperative pain management after cesarean delivery.

Locoregional analgesia

During anesthesia for cesarean delivery, central neuraxial techniques outnumber general anesthesia in many countries. Besides the benefits associated with postnatal adaptation of the mother and child, another indisputable advantage is that when using continuous epidural techniques, it is possible to use the inserted epidural catheter for postoperative analgesia. It is beneficial to combine opioid analgesics (mostly sufentanil) and local anesthetics (for doses see section 6.3). If a single-injection epidural anesthesia is used, it is preferable to combine it with a long-acting opioid analgesic (preservative-free morphine, optimal dose is 3–4 mg). Similarly, the duration of analgesia during spinal anesthesia may be prolonged by adding a small dose of preservative-free morphine, doses above 0.2 mg usually do not lead to a better effect. It should be noted that opioid analgesics, morphine in particular, cause itching (pruritus) in a large percentage of these patients. Locoregional techniques of anesthesia and analgesia may be safely used during other surgical procedures on breastfeeding women as well. Wound infiltration and/or abdominal nerve blockades reduce the analgesic requirement, but only on the first postoperative day.

Systemic analgesia

Paracetamol, single-dose fentanyl, morphine in normal doses, and ibuprofen (except for analgesia after cesarean delivery due to a higher risk of bleeding) are considered safe in systemic analgesia during lactation. Medications with unknown adverse effects to be used with caution include benzodiazepines, antidepressants, continuous administration of fentanyl and sufentanil, and most nonsteroidal anti-inflammatory drugs (NSAIDs).

Not recommended or contraindicated drugs are acetylsalicylic acid, pethidine (long-term administration leads to neurobehavioral changes in infants), and indometacin.

Note: Codeine is no more recommended. A fatal respiratory depression has been reported in an infant, whose mother took analgesics containing codeine during lactation and belonged to a rare group that rapidly metabolizes codeine to morphine. Recently, FDA issued warning that tramadol should not be used to treat pain in all children younger than 12 years and in children younger than 18 years after the removal of tonsils and/or adenoids. No such warning was given by the European Medicines Agency and other authorities.

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10

Postoperative pain management in patients with chronic pain on long-term opioid therapy

10.1 Definition of chronic pain (CP)

Chronic pain is a pain that lacks the biological signal value and persists past the normal time of healing, which is usually taken to be 3 months. Unlike acute pain, CP is not a mere symptom – it is currently considered a disease *sui generis*.

10.2 Characteristics of patients with CP

Approximately 19% of the adult population in Europe suffers from CP of medium to high intensity, which significantly limits their daily activities and has a social impact. The most common diagnoses of CP are: back pain, joint pain, headache, neuropathic syndromes, visceral pain, chronic postoperative and post-traumatic pain. Patients with chronic pain can be characterized by anxiety, depression, reduced overall functional capacity, and psychosocial and economic factors also play a major role. An increased requirement of postoperative analgesia should be assumed in all patients with CP. A complex pain therapy is common – non-opioid analgesics, opioids, and a whole range of co-analgesics (adjuvant analgesics), such as antidepressants, anticonvulsants, benzodiazepines, centrally-acting muscle relaxants, corticosteroids, alpha-2 agonists, etc. All of these drugs may produce significant interactions throughout the perioperative period. A specific issue is the increasing number of patients on long-term opioid therapy (see below). CP can be divided into cancer pain and non-cancer pain. The treatment strategy for both types of CP is virtually identical. The treatment is generally determined by the intensity of pain.

10.3 Current guidelines for CP treatment (in relation to postoperative pain management)

10.3.1 Pharmacotherapy

The basic algorithm for CP pharmacotherapy is the three-step analgesic ladder developed by the WHO, where the general idea is to start with Step 1 drugs, and then climb the ladder if pain persists ("step up"). Mild pain should be treated with non-opioid analgesics (Step 1). If pain relief is not achieved (moderate pain), weak opioid analgesics should be added (Step 2). If this is not sufficient (severe pain), weak opioids are replaced with strong opioids (Step 3). The analgesic ladder also includes the possibility of adding adjuvant analgesics (co-analgesics), which may be effective in some types of pain, and auxiliary drugs designed to treat the side effects of analgesics. A reverse direction ("step down") applies to pharmacotherapy of acute pain, including postoperative pain.

WHO analgesic ladder

		Step 3 – severe pain
	Step 2 – moderate pain	
Step 1 – mild pain	Weak opioids	Strong opioids
Non-opioid analgesics	+ Non-opioid analgesics	+/– Non-opioid analgesics

10.3.2 Interventional pain management

Interventional pain management including radiofrequency treatment and neuromodulatory techniques has been increasingly used in patients with refractory CP. An essential prerequisite for successful interventional pain management is the diagnosis of pain and its origin. Radiofrequency treatment can provide either long-term interruption of afferent pathways (radiofrequency thermal lesion) or affect their functionality (pulse radiofrequency).

There are two basic neuromodulatory techniques:

- stimulation techniques – peripheral nerve stimulation and spinal cord stimulation (non-pharmacological methods)
- implantable drug delivery system used mainly for intrathecal administration of morphine

10.4 Postoperative pain management in patients on long-term opioid therapy

Opioid analgesics have the highest analgesic potential and constitute a fundamental pillar of severe pain management. Currently, the indications for opioid analgesics have expanded to include refractory chronic non-cancer pain. The number of patients treated with opioids has increased and will continue to rise. Anesthesiologists need to keep in mind that patients on long-term opioid therapy have different reactivity, altered pain threshold, and usually increased postoperative analgesia requirements.

10.4.1 Specific factors of opioid therapy

Mistaking important concepts (dependence, tolerance) can frequently cause an incorrect interpretation of the clinical condition and consequently lead to inadequate postoperative pain management.

Tolerance
Tolerance is a pharmacological concept describing the need to increase the dose of opioids in order to maintain the initial analgesic effect. While tolerance to certain adverse effects (nausea, vomiting, sedative effect, impaired cognitive functions, respiratory depression) develops rapidly, tolerance to the analgesic effect develops relatively slowly. Tolerance to miosis and constipation is virtually non-existent. However, the need to increase the dose due to an insufficient analgesic effect is mostly related to a progression of the underlying disease. Nevertheless, it is necessary to be aware of the possibility of developing tolerance to opioids. An opioid-tolerant patient has different requirements for postoperative pain management than patients who had never used opioids (opioid-naive).

Physical dependence
Physical dependence is an adaptive state characterized by the development of withdrawal syndrome upon a significant reduction in the dose of opioids, or after an abrupt discontinuation of opioid therapy. Withdrawal syndrome may also develop during treatment with μ-opioid agonists after the administration of an opioid from the group of agonists-antagonists (butorphanol, nalbuphine, pentazocine), partial agonists (buprenorphine), or opioid antagonists (naloxone, naltrexone). It is characterized by the hyperactivity of the sympathetic nervous system – anxiety, increased irritability, decreased pain threshold, sweating, nasal discharge, lacrimation, piloerection ("goose bumps"), nausea, vomiting, yawning, mydriasis, abdominal colic, hypervigilance, hypertension, tachycardia, arrhythmia, paroxysmal spasms. Withdrawal syndrome must not be confused with addiction. *In clinical practice, every patient on long-term opioid therapy should be regarded as physically dependent!* Withdrawal syndrome may often have an iatrogenic cause – unwise discontinuation of opioid therapy, opioid rotation, or a change in the route of administration, irrespective of adequate equianalgesic doses (Table 10.1). Clinical symptoms of withdrawal syndrome are suppressed by alpha-2 agonists, beta-adrenolytics, benzodiazepines, and opioids, of course.

Psychological dependence – addiction
Addiction is a complex bio-psycho-social phenomenon, with a specific behavioral pattern characterized by a compulsive craving and pathological desire to take the substance despite its adverse medical, psychosocial, or existential implications. Patients typically lose control over the use of this drug and do not take the opioid for pain relief, but for its euphoriant, psychogenic effect. However, the mere administration of a drug with a potential risk of developing addictive behavior is not sufficient to develop psychological dependence. Besides exposure to the substance, there are several other factors necessary to develop a psychological dependence on opioids: a sensitive individual with a certain biogenetic and psychological predisposition, a typical social context, and the absence of pain. Typical symptoms of addictive behavior are: forging prescriptions, injecting drugs that are prescribed for oral or transdermal administration, non-compliance and modification of the treatment without the doctor's approv-

al, simultaneous uncontrolled alcohol and drug abuse, consultation of other physicians to obtain opioid prescriptions, repeated loss of prescriptions and medications, sometimes emphasizing an allergy to non-opioid analgesics, codeine, or local anesthetics ("only an opioid, such as pethidine, will always help"), patient "in a hurry", etc.

Pseudo-addiction
Sometimes the patient desperately asks for an increased dose of analgesics due to insufficient analgesia. Medical personnel may describe this situation as a typical manifestation of addiction. However, after an appropriate adjustment of dosage, the patient calms down.

Opioid-induced hyperalgesia
Paradoxically, patients on long-term opioid therapy can sometimes have a reduced pain threshold. This condition is referred to as opioid-induced hyperalgesia and is evident in withdrawal syndrome. Due to the development of postoperative hyperalgesia, patients on long-term opioid therapy should not receive remifentanil intraoperatively (see section 6.2.2).

10.4.2 Choice of postoperative analgesia

Even in patients on chronic opioid therapy, opioid analgesics are an important component of postoperative analgesia. Throughout the perioperative period, patients should receive maintenance doses of opioid, which they are accustomed to in the long term. Knowledge of equianalgesic doses of opioids in relation to their routes of administration is crucial. A suitable opioid for calculations with equianagesic doses and routes of administration is morphine. Morphine is considered a reference opioid, as it is the cheapest one and with the largest clinical experience. Another suitable option is piritramide. In intensive care, fentanyl and sufentanil may also be administered. Pethidine is considered an obsolete opioid (highest incidence of nausea and vomiting, neurotoxic metabolites, psychotomimetic potential). It is often very difficult to achieve high-quality analgesia in this group of patients. Therefore, it is beneficial to use the entire spectrum of multimodal analgesia including non-opioid analgesia (opioid-sparing effect), as well as locoregional analgesia techniques, which are irreplaceable in this respect. In opioid-tolerant patients, several other analgesics and co-analgesics (ketamine, clonidine, dexmedetomidine, gabapentin) may play an important role. In the postoperative period, it is also necessary to ensure an adequate transition to chronic therapy.

Approach to opioid-tolerant patients
Preoperative period
1. Evaluate current opioid therapy – diagnosis of pain, daily dose, tolerability.
2. Ensure continuity of opioid treatment – do not remove transdermal opioids, keep morning oral doses of opioids, or replace them with equianalgesic parenteral doses (table 10.1).
3. Evaluate ECG – watch out for bradycardia under 60/min and QT interval above 0.440 ms – increased risk of arrhythmias.
4. Keep the basal dose in patients with continuous opioid intrathecal analgesia (spinal pump).
5. Treat patients as people with a full stomach.

Intraoperative period
1. Provide a continuous dose of opioids – do not remove transdermal opioids (beware of warming systems with a risk of direct contact with the transdermal system and subsequent rapid absorption of the opioid), IV continuous dose of opioids, intrathecal administration of opioids.
2. Assume increased requirements for the opioid component of general anesthesia, which may increase by 50–300%.
3. After recovery from anesthesia, adequate level of opioids is assumed if the frequency of spontaneous respiration is 12–14/min and mild miosis is present.

Postoperative period
1. The plan for postoperative pain management should be prepared before the surgical procedure.
2. Preference is given to continuous IV opioid analgesia, ideally in the PCA mode (patient-controlled analgesia), and locoregional analgesia techniques.
3. Keep a basal dose of systemic opioids even if locoregional analgesia is used. Beware of respiratory depression, as pain that stimulates ventilation is reduced by the locoregional blockade! Avoid withdrawal syndrome upon a drastic reduction in the daily dose of opioids or upon a complete discontinuation of opioid therapy. About 25% of the original total daily opioid dose will prevent the development of withdrawal syndrome in most cases.
4. Use multimodal analgesia – administer non-opioid analgesics according to a schedule, or already during surgery: IV paracetamol, IV metamizole, IV COX-2 selective inhibitors – parecoxib, IV NSAIDs – diclofenac, etc.
5. If the indication for opioids no longer exists thanks to the surgical treatment (e.g. hip replacement), it is advisable to prolong the usual postoperative opioid analgesia and gradually reduce the dose by 25% every 2–3 days and attempt to discontinue opioid therapy. However, the gradual withdrawal of opioids usually takes much longer. Cooperation with an anesthesiologist – pain specialist is recommended.

Equianalgesic doses of strong opioids in mg/24h
The gold standard for the comparison of other drugs is analgesia induced by 10 mg of morphine SC. The doses in this table are approximate and should be adjusted according to interindividual differences (age, current level of pain, duration of opioid therapy, side effects, sensitivity to opioids, route of administration, new opioid in case of opioid rotation – see methadone, etc.). These factors should be taken into account and the calculated dose should be modified accordingly. With highly lipophilic opioids (sufentanil, fentanyl, alfentanil) administered parenterally, the effect of a bolus dose is given.

Table 10.1 Equianalgesic doses of strong opioids (recommended by the Society for the Study and Treatment of Pain)

Morphine SC	10	20	30	40	50	60	80	100	200
Morphine PO[1]	30	60	90	120	150	180	240	300	600
Morphine epid.[2]	3.0 (2.0)	6.0 (4.0)	9.0 (6.0)	12 (8.0)	15 (10)	18 (12)	24 (16)	30 (20)	60 (40)
Morphine IT [3]	0.15–0.3 (0.2)	0.6 (0.4)	0.9 (0.6)	1.2 (0.8)	1.5 (1.0)	1.8 (1.2)	2.4 (1.6)	3.0 (2.0)	6.0 (4)
Fentanyl TTS mcg/h	12.5	25		50		75	100	125	250
Fentanyl TTS mg/24 h	0.3	0.6		1.2		1.8	2.4	3.0	6.0
Oxycodone PO	20	40	60	80	100	120	160	200	400
Tapentadol PO	100	200	300	400	500				
Buprenorphine IM	0.3	0.6	0.9	1.2	1.5	1.8	2.4		
Buprenorphine TDS mg/24 h			0.84	1.26		1.68			
Buprenorphine TDS mcg/ h			35	50		70			
Hydromorphone IM	1.5								
Hydromorphone PO	4	8	12	16	20	24			
Pethidine (meperidine) IM	100								
Methadone IM	10								
Methadone PO[11]	20								
Piritramide IM	15	30	45						
Fentanyl IV [22]	0.1								
Fentanyl IT [33]	0.0375–0.075								
Alfentanil IV [22]	0.75								
Sufentanil IV [22]	0.010–0.015								
Sufentanil IT [111]	0.0125–0.025								

[1] Applies to regular oral (PO) dosing of morphine SR (ratio 1:3), for a single-dose administration the ratio is 1:3–6; 10 mg of morphine SC (subcutaneous) corresponds rather to 60 mg of morphine SR.

[2] The value in brackets corresponds to the situation when morphine is administered together with bupivacaine 0.125%. When the daily dose of morphine epid. (epidurally) exceeds 40–60 mg, it is rather a systemic administration due to the high serum concentrations and this route of administration loses its sense and benefits compared to SC administration.

[3] Morphine administered intrathecally (IT) is approx. 100–150 times more potent than morphine PO. The value in brackets calculates with 150x higher potency and is recommended as the initial dose when switching from systemic opioid to IT morphine (opioid rotation). IT morphine is 10–20 times more potent than morphine epid. The usual sufficient dose of IT morphine for postoperative analgesia is 0.1–0.3 mg.

[11] Applies to a single-dose administration, does not apply to switching from another opioid (opioid rotation) to methadone. In that case, the proper dose is much lower (approx. 5–7.5 mg) and it must be established by individual titration with daily monitoring.

[22] The analgesic potency of a bolus administration.

[33] Fentanyl IV has approx. 100 times higher analgesic potency than morphine, but when administered intrathecally, its relative potency in comparison with IT morphine is only 4 times higher. The effect lasts for 2–4 hours.

[111] Sufentanil IV has 650–1000 times higher analgesic potency than morphine, but when administered intrathecally, its relative potency in comparison with IT morphine is only 8–16 times higher (the conversion calculates with 12 times higher potency). The effect lasts for 2–4 hours.

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11

Postoperative pain management in the elderly

11.1 Specifics of the group

The number of surgical procedures in geriatric patients is increasing in both absolute and relative terms. Elderly patients do not form a homogeneous group, as interindividual differences increase with age. The biological age is more important than the chronological age. Aging brings about both physiological changes (loss of neurons, thinning of the myelin sheath, changes in the secretion of neurotransmitters and changes at receptor level, changes in the volume of distribution, hypoproteinemia, decreased performance of parenchymal organs) and pathophysiological changes (dementia, complicating diseases). Comorbidity and polypharmacy are common in old age. An increased sensitivity to drugs affecting the CNS has been reported in the elderly and postoperative delirium is more common in geriatric patients than in younger ones. It may be caused both by some analgesics (inducing central anticholinergic syndrome), or by pain due to insufficient analgesia. On the other hand, nausea, vomiting, and itching induced by opioid analgesics are less frequent. In comparison with younger population, there is a lower risk of developing chronic postoperative pain. Pain assessment using conventional methods (visual analogue scale - VAS) may be more challenging in the elderly, as well as using patient-controlled analgesia. Numeric Rating Scale 0–10 (NRS) is preferable to VAS. Facial expression scale, which is used in children, may be employed as well. In non-communicating patients, it is difficult to estimate the intensity of pain (monitoring grimaces, vegetative signs, or deviations from their stereotype of behavior). It has been demonstrated that elderly patients ask for painkillers less often than younger patients. Proper dose should be adjusted by titration.

11.2 Possible techniques

While virtually all techniques of postoperative pain management may be applied, it is necessary to reduce the dose of the medication used (e.g. the dose of morphine should be half the standard dose; in general, the dosing intervals extend as well). When administering opioid analgesics, it is advisable to use intravenous administration by careful titration. Renal insufficiency leads to an accumulation of metabolites: norpethidine, morphine-3-glucuronide, morphine-6-glucuronide, and desmethyltramadol. Multimodal analgesia reducing the opioid requirement is beneficial and preference is given to locoregional analgesia techniques. Non-pharmacological methods may reduce the demands on pharmacotherapy (positioning, thermal comfort, early individualized rehabilitation). The safety and quality of postoperative pain management in the elderly is dependent on a careful monitoring of these patients.

11.3 Not recommended and contraindicated techniques

After 65 years of age, the toxicity of NSAIDs increases significantly (gastropathy, nephrotoxicity, cardiovascular toxicity, coagulopathy). While their short-term administration is not contraindicated, non-opioid analgesics, such as paracetamol or metamizole, are preferred. Ketamine is not recommended due to a higher risk of psychotomimetic effects. When using other medications, it is necessary to pay attention to contraindications or limitations arising from complicating diseases and drug interactions (see section 6.2.2).

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12

Postoperative pain management in ambulatory surgery

12.1 Specifics of the group

Ambulatory surgical procedures offer many benefits to patients, and their number continues to rise. Proper selection of high-quality postoperative analgesia is of particular importance in outpatients, since strong postoperative pain, as well as adverse effects of the therapy, such as severe postoperative vomiting, are along with surgical complications among the most common reasons for unplanned hospitalization. A specific feature of ambulatory surgery is that it mostly concerns patients classified as ASA I–III, the procedures predominantly do not involve the opening of body cavities (although laparoscopic cholecystectomy is increasingly performed as a day surgery), and significant blood loss is not expected. Another requirement is to have an easily accessible contact for a health care facility, assistance of an instructed person in the postoperative period and a good accessibility of medical care.

12.2 Preoperative measures

Patients should be given instructions on postoperative pain management in advance, preferably in writing, and they should be provided with the necessary medication beforehand. The instructions should involve not only dose, but also the expected level of pain, possible side effects, and contact information for a physician in case of questions or issues that may arise after discharge. In general, any type of premedication may be used. In practical terms, it is advisable to avoid long-acting sedatives and medication that potentiates nausea and vomiting. Some authors recommend routine administration of antiemetics as part of premedication.

12.3 Intraoperative measures

There are no specific recommendations. The anesthesiologist should ensure that the patient does not feel pain after recovery from anesthesia, especially if only inhalational anesthesia or short-acting opioids (remifentanil) were used. A great advantage is that it is possible to use a peripheral nerve blockade with a long-acting local anesthetic, but it is necessary to use a lower concentration to reduce the motor blockade (recovery of motor function is a necessary condition for discharge). Neuraxial blockades should be used only in fully informed patients familiar with the symptoms of potential complications associated with these techniques. Low doses are used to ensure rapid regression of the blockade – therefore, they are of little significance in postoperative analgesia. Spinal administration of opioids should be avoided.

Widely recommended measures include wound infiltration with a long-acting local anesthetic performed by the surgeon at the end of the procedure.

12.4 Postoperative measures

A prerequisite for postoperative pain management in the home environment is the administration of oral medication only. The patient leaves the health care facility with an established and fully functional analgesic regimen and is familiar with the rescue procedure to be followed in case of failure of the established regimen (weak opioid at the upper limit of the recommended dose range as a supplement to regular doses of a non-opioid analgesic together with a nonsteroidal anti-inflammatory drug – NSAID). Intense postoperative pain is one of the reasons for unplanned hospitalization after ambulatory surgery. It is generally recommended to use multimodal analgesia including a combination of locoregional techniques and systemic analgesics, as well as suitable non-pharmacological methods. Patient education about the appropriate method of positioning, rehabilitation, physical factors, etc. is common with sports injuries, while in ambulatory surgery it is often neglected. In primary systemic therapy, the commonly recommended doses and combinations of non-opioid analgesics (1 g of paracetamol PO every 6 hours), NSAIDs (e.g. diclofenac 75 mg every 8–12 hours), and weak opioids may be used. An alternative option to nonselective COX inhibitors is to use coxibs – see section 6.2.2. The necessity of using strong opioids implies hospitalization in many countries.

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13

Organization of postoperative pain management

13.1 Introduction and integration of postoperative pain management into multidisciplinary patient care

Acute and postoperative pain management is one of the main criteria for assessing the quality of health care and patient satisfaction. The number of patients in whom we must assume the need for postoperative pain management equals the number of patients undergoing surgical or diagnostic procedures. The total amount of major surgical procedures worldwide is estimated at 234 million per year. This means that postoperative pain management concerns approx. 3.3% of the world population annually.

The treatment of acute pain is in focus of various professional societies, societies for the accreditation of health care facilities, and government authorities responsible for health care around the world. They set out best practice, introduce minimum standards of pain management that health care facilities must meet to be allowed to provide health care, provide resources for the establishment of functional organizational schemes of acute pain management, for their assessment and further development. Guidelines on pain management have been issued by a number of professional societies and are easily accessible. The minimum requirements outlined in the standards of accrediting organizations such as JC include monitoring of pain and a documented reaction to the measured value.

Safe and effective acute pain management requires:

- appropriate education of all health care professionals (anesthesiologists, surgeons, nurses, pain specialists, and general practitioners)
- high-quality organization of acute pain management at the health care facility
- comprehensible and adequate patient education

Health care professionals need to realize that postoperative pain management is an integral part of patient care, and that untreated pain is a sign of professional incompetence. The patient must be informed about treatment options and the associated risks before surgery. In the preoperative period, the patient must be familiarized with the perioperative analgesic procedure, methods of pain assessment (see Chapter 4), and further therapeutic options if the pain persists. Patients should be encouraged to talk about their pain with the personnel and demand procedures that will bring pain

relief. Health care professionals providing care on wards where patients are treated for pain should have sufficient knowledge on the diagnostics and treatment of pain. Bedside nurses play a key role, as they spend more time with the patient than any other health care professionals. Adequate education and medical functions delegated by physicians to nurses within firmly established rules increase the interest of bedside nurses in the issue and improve the overall results of pain management.

A high-quality organization of pain management at a health care facility includes:

- pain assessment,
- treatment guidelines,
- patients monitoring guidelines,
- guidelines for the treatment of potential complications,
- education,
- system for evaluating the success of organizational and therapeutic measures (audits),
- high quality standard of medical documentation

These factors are often more important than advanced pain management techniques without good quality organization of pain management. Even simple analgesic procedures in the hands of educated personnel that works under the established rules can lead to good pain relief. After mastering basic techniques and setting the rules for the provision of acute pain management, advanced techniques for the treatment of acute pain may be introduced.

Acute pain management should be viewed as one piece of a mosaic composed of perioperative and postoperative care. In addition to well-organized and performed acute pain management, it involves further optimization of perioperative procedures, such as suitable pre- and postoperative nutrition, adequate and sufficient physiotherapy, minimally invasive surgical techniques (see Chapter 14). Fast and effective techniques of perioperative and postoperative care are summarized e.g. in Enhanced Recovery After Surgery (ERAS) guidelines, and high-quality analgesia is seen as an integral part of them. Many of these methods require a major shift in thinking and doing of all participating health care professionals. One of the main challenges when new organization of acute pain management is being introduced or changes are being made to the peri- and postoperative care are the established stereotypes, power struggles among the individual participating health care professionals of various specialties, and a lack of will and resources to change the situation. A high-quality model of acute pain management requires prescriptive decisions at the level of the hospital management, clearly defined rules and adherence to them.

Postoperative pain management should be integrated in the continuous improvement of the quality of care. A system of measuring its results through clinical audits should be set up. The system of acute pain management becomes incorporated into the quality management of the facility, together with similar projects improving the quality and safety of provided care, such as the prevention and control of hospital acquired infections, prevention of medication errors, prevention of patient identification errors or wrong site surgery, etc.

13.2 Objectives of postoperative pain management

Pain management aims to effectively alleviate or eliminate pain with minimal adverse effects and as cheaply as possible.

It entails an effective and safe elimination of pain and the associated stress reaction, enabling early mobilization and physiotherapy, prevention of both peripheral and central sensitization, prevention of primary and secondary hyperalgesia and thus the transition from acute to chronic pain. An adequate acute pain management reduces the frequency of certain complications (respiratory infections, urinary retention, impaired motility of the gastrointestinal tract), reduces the cost of hospitalization and increases patient satisfaction with hospitalization (as one of more independent factors).

13.3. Basic rules for acute postoperative pain management

- treatment of pain is one of the fundamental human rights of the patient
- decent and safe analgesia for all patients
- postoperative pain management is a continuation of the analgesic component of general anesthesia, or a follow-up to regional anesthesia
- there are significant interindividual differences in response to analgesic treatment and in pain tolerance, the patient's report of pain is crucial in pain monitoring ("believe your patient, the pain is what the patient says it is")
- preference is given to multimodal pharmacotherapy (in order to reduce the adverse effects of the individual drugs) and combined therapy (systemic therapy + locoregional anesthesia)
- it is necessary to prescribe "rescue" medication and specify the steps to be followed if the prescribed analgesic therapy is not sufficient, there always has to be another option if the present treatment does not work well
- creation and adoption of algorithms for pain management procedures based on the type of surgery and the anticipated level of postoperative pain is recommended (procedure-specific analgesia)
- pain and the adverse effects of pain management are monitored, the values are recorded in the documentation, and conditions outside the agreed normal range are treated; the pain assessment scales and assessment of adverse events are an integral part of the documentation, every health care professional knows where to find them. The intensity of pain, the effectiveness of treatment and the occurrence of any complications are monitored. They are recorded regularly, in the early postoperative period at least 4 times a day. Make the pain visible.
- there have to be established procedures to address the adverse effects of acute pain management (procedures for respiratory disorders, impaired consciousness, complications of regional analgesia, etc.).
- there are local hospital-wide guidelines for monitoring pain, pain management, and for the treatment of the associated adverse effects
- preparation and dilution of analgesic formulations are included in the approved protocols for the health care facility
- rules for the treatment of specific patient populations (chronic pain patients, comatose patients, children, the elderly, drug addicts, etc.).
- high-quality organizational structure of care (who is supposed to do what, how they are supposed to do it, who should they consult if they do not know what to do in a given situation)
- health care professionals involved in pain management need to have well-defined competencies and functions
- multidisciplinary collaboration is advisable (bedside nurse, attending physician, anesthesiologist, physiotherapist, clinical pharmacist, and an APS nurse and physician if there is an APS system)
- continuing education of physicians and nurses in pain management
- routine patient education about pain monitoring and pain management
- a health care professional or a team should be appointed to supervise acute pain management at the department or health care facility
- regular meetings of professionals appointed to organize acute pain management, meetings of these professionals with other health care professionals involved in the treatment of acute pain
- the results of acute pain management are assessed in audits, a register for acute pain management may be introduced in order to collect data on acute pain management at the department or at the whole health care facility. This data can then be used for benchmarking of departments or health care facilities.

13.4. Pain as the fifth vital sign

This concept views postoperative pain as the fifth vital sign. Vital signs traditionally include blood pressure, pulse, respiratory rate, and body temperature. In intensive care, blood pressure, pulse, respiratory rate, and consciousness are considered vital signs. Strictly speaking, pain is not a vital function, it is a symptom. Nevertheless, in an effort to attract the attention of health care professionals towards patients in pain and to simplify pain assessment and monitoring, it is viewed as one of the vital signs, which needs to be measured. If the measured value lies outside the specified range, treatment is initiated so as to normalize the values. This concept is particularly suitable for medical personnel education. The concept of pain as the fifth vital sign is facing objections recently, especially when monitoring leads to abundant opioid prescription in patients with chronic pain. This can be an issue in some countries or parts of the world. In the case of acute postoperative pain, the authors in accordance with the opinion of professional pain societies regard the concept of the fifth vital sign as a useful tool in improving the everyday practice of pain monitoring and treatment.

When treating acute pain, especially if opioid analgesics are administered, medical personnel should monitor not only pain, but also any potential adverse effects associated with acute pain management. If opioids are used, the most sensitive marker of opioid overdose is a reduced respiratory rate and sedation. In this respect, monitoring respiratory rate and the level of consciousness is crucial. Level of consciousness may be assessed using e.g. the Ramsay scale. The pain management protocol also includes any warning values of vital signs and a recommended procedure for addressing complications, such as the immediate administration of naloxone 0.1–0.4 mg IV if the respiratory rate drops below 8 breaths/min and if a dangerous level of sedation is observed – the patient is difficult to arouse (Ramsay score 5), etc.

Table 13.1 Ramsay scale

Score	Clinical description
1	Patient is anxious, agitated, restless
2	Patient is cooperative, oriented, tranquil
3	Patient responds to commands only
4	Patient is asleep and exhibits brisk response to light glabellar tap or loud auditory stimulus
5	Patient is asleep and exhibits a sluggish response to light glabellar tap or loud auditory stimulus
6	Patient is asleep and exhibits no response

Similar guidelines need to be developed for other potential complications associated e.g. with regional analgesia. The level of the block and movement of limbs should be monitored. If higher doses of paracetamol are used over several days, liver function tests should be obtained. When administering higher doses of NSAIDs, renal functions should be monitored.

13.5 Organization of postoperative pain management with an Acute Pain Service (APS)

A permanent acute and postoperative pain service (APS) is seen as the most suitable way of ensuring high-quality organization of pain management. This concept is based on multidisciplinary patient care supervised by a dedicated team. The attending physician is responsible for the overall care and care within their specialty. However, other health care professionals also engage in the treatment process and address the various aspects of the patient's condition in more depth. In modern medicine, one person (the attending physician) is usually not capable of mastering all the procedures and treatment options available for the optimal patient care. Therefore, physiotherapists and nutrition specialists are also involved in patient care, the medication is checked by a clinical pharmacist, and an APS physician and nurse are engaged in acute pain management. The APS team offers continuous consultation for health care professionals of all specialties and takes care of patients using special analgesic techniques. APS physicians are invited to complex cases or complications of the treatment.

The main **benefits of implementing the APS** lie in the continuity of care for patients with acute pain, better organization of postoperative pain management within the health care facility, resulting in a lower level of pain and minimization of the occurrence of stress response to pain. This leads to a reduction in postoperative complications, faster mobilization, shorter hospitalization, and ultimately to a reduction in treatment costs.

Requirements for the implementation of the APS involve the setting up of an APS structure suitable for the given health care facility. The main conditions for implementing the APS are as follows:

- the APS is established by a decision of the health care facility management which shall have a compulsory effect for all specialties; the APS is usually supervised by the department of anesthesiology.
- establishing the APS team – appointing nurses and physicians as members of the team
- training of health care professionals of all specialties in the principles of the APS and pain management
- defining the competencies and duties of the APS team, defining the competencies and duties of other medical personnel in acute pain management
- developing and adopting analgesic guidelines
- creating and approving documentation for monitoring and treating pain, or modifying the current documentation
- preparing patient education materials

Before drawing up pain management and organizational guidelines and before the APS team actually starts to work, it is advisable to conduct an audit of current practice in acute pain management to obtain reference data for the subsequent evaluation of the changes after the implementation of the APS.

Organizational models of the APS and APS nurse competencies

There are basically two types of APS organization: an APS conducted by an APS physician (physician-based APS) and an APS conducted by a nurse supervised by an APS physician (nurse-based, physician-supervised APS). Ideally, the APS team is available 24 hours a day, 7 days a week. If human resources are limited, an anesthesiologist and/or a nurse anesthetist on duty (nightshift, weekends) or another dedicated person might be used for APS purposes. Time schedule of the APS team should always be organized with respect to the needs of the particular health care facility, while taking into account personnel and financial costs. All health care professionals involved in acute pain management have clearly defined competencies and functions and work in accordance with the established communication rules of the team.

Standardly, the bedside nurse addresses the patient's pain, under professional supervision of the attending physician of the department. The APS nurse makes rounds on the patients with pain several times a day, focusing on patients with advanced analgesic techniques (regional analgesia, PCA) and patients with difficulties in pain management (inadequate response to analgesics, contraindications for the administration of certain analgesics, etc.). Methodically, the APS nurse is guided by the APS physician and consults any problematic issues with the APS physician.

Material provision and documentation

To implement the APS, the following material conditions must be met:

- resources for the APS personnel (nurse and physician),
- medication,
- equipment (advanced techniques of acute pain management),
- establishment and appropriate modification of medical documentation that takes into account the need to monitor acute pain and potential adverse effects of the treatment (see Section 13.4 and Appendix 1).

The APS team keeps their own documentation for their needs. The documentation serves to collect data necessary for daily operations, to evaluate the work done by the APS team over a longer period of time and to subsequently process the data in order to evaluate the results of acute pain management. The APS nurse (physician) has a pager or a hospital mobile phone with one number. Contact information of the APS team must be available at all departments.

An example of a possible definition of competencies and rules of communication for the various health care professionals within the APS system, as well as rules for prescribing and monitoring the treatment of acute pain and the associated adverse effects are given in Appendix 2.

In general, the system of acute pain management under the APS supervision should always be defined by compulsory documents with a hospital-wide effect and the procedures specified in the documents should be obligatory for all health care professionals.

An important factor for the implementation of the APS in a health care facility is the compliance of staff to the system. A suitable model of medical personnel education is of utmost importance. Education is not a one-time training at the time of the APS implementation, it must continue in the following period as well. Low compliance of medical personnel can result in the reluctance to let the APS team consult medical documentation and recommend changes in the established acute pain management procedures. This can be avoided by introducing compulsory rules and guidelines and by appropriate education. Significant risks of implementing the APS include the efforts of other specialties to completely get rid of acute pain management and delegate it to the APS team. Another issue is the economic aspect – immediate costs versus long term savings. The implementation costs vary primarily according to how advanced techniques the health care facility chooses to use. The actual implementation of the APS requires mostly just personnel costs (APS nurse or physician). A functional APS system leads to cost savings at the level of the whole health care facility in the long term. The main mistake is to develop and use a single procedure for all types of pain, or the other way round, to develop too many complicated procedures for postoperative pain management. Another challenge might be the adherence to the officially approved use of certain medications. Modern methods of acute pain management are sometimes ahead of the current pharmaceutical guidelines, maximum daily doses, etc. and drugs may be administered outside their approved indication (off-label).

Future of the APS

Thanks to the APS, new concepts and trends in acute postoperative pain management and in the organization of care for patients with acute pain are emerging. They can be summarized in several areas. These concepts require an already established and functional APS system.

1. Creation of specific guidelines for defined patient populations and procedures. This concept is based on the fact that with certain clearly defined procedures in an average patient, the level of pain may be predicted fairly accurately, and thus pain management techniques may be simplified and refined.
2. Acute and postoperative pain management as a process of continuous quality improvement in the health care facility.
3. Point 2 is closely related to the process of creating databases and benchmarking. This approach has been adopted from the corporate sector and in general, it consists in quality improvement based on creating databases containing results of the processes (in our case – results of postoperative pain management) and their comparison across companies (across different health care facilities) or against best practice. Various hospitals around the world have registers of acute pain management, which gather data on the results of the established procedures. In recent years, there has been an effort to compile national and multinational multicentric registers.

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14

Future perspectives of postoperative pain management

It has been repeatedly stated that for about half a century there has been no breakthrough technique or medication for the treatment of acute postoperative pain. On the contrary, several promising methods have temporarily disappeared from the market (e.g. iontophoretic administration of fentanyl, available again since 2015), other new methods that might work are only indicated for breakthrough pain in cancer patients and the Summary of Product Characteristics (SPC) explicitly states that they contraindicated for the treatment of acute pain (transmucosal forms of fentanyl), many other more or less established methods of acute pain management use medications in indications and routes of administration, for which they are not approved (e.g. adding clonidine to local anesthetics). New techniques that are being tested include inhaled intranasal and transpulmonary administration of opioids, there is an increasing number of studies on the systemic administration of lidocaine during intra-abdominal procedures, and new devices enable patient-controlled regional (intra-articular and perineural) analgesia. Another new technology enables the use of catheters for continuous administration of a local anesthetic directly into the surgical wound and new forms of established medications (long-acting local anesthetics and opioid analgesics, a combination of opioid analgesics and drugs that suppress their adverse effects on the gastrointestinal tract, etc.). By contrast, cannabinoids do not seem to find their use in acute pain management.

On the other hand, many renowned authors suggest that there is no need to seek new methods and techniques. Thus, it seems that in the future we can expect improvements mainly in the organization of perioperative care and in comprehensive involvement of all medical personnel in postoperative pain management. A new concept of Perioperative Surgical Home is being introduced, logistically led by anesthesiologists. This model is centered on the individual needs of the patient, from the preparation for surgery to discharge from the hospital. First such facilities have already appeared.

It is important to determine what is the aim of perioperative treatment. A narrow focus on just one issue – high-quality analgesia – will not lead, on its own, to an improved postoperative course and quality of life after surgery. This narrow focus has been recently identified as a quest for the holy grail of anesthesiology and pain management. Numerous studies have confirmed that patient satisfaction with the treatment is a multifactorial experience and the actual intensity of postoperative pain is only one of many components, along with empathy of the personnel, the speed at which the patient receives an analgesic, the onset of action of pain medication, the absence of complications, etc. This may also be a cause of disappointment when the patient does not positively evaluate a highly sophisticated and effective analgesic technique and complains about its side effects that are insignificant from the point of view of the medical personnel. Only a combined approach involving the whole team that takes care of the patient during the surgical treatment will ultimately lead to a better overall outcome. Examples include the implementation of ambulatory and minimally invasive surgery, effective rehabilitation, early initiation of oral food intake, patient education, stress reduction, etc. Indeed, many APS teams in the world provide not only postoperative pain management, but also take care of nutrition and other factors of complex well-being, thus forming perioperative care teams. As for the future of pain management procedures, it is necessary to weigh the risks and benefits of any particular method with regard to patient compliance, but also considering the benefit-cost ratio. It is possible that the use of long-acting local analgesics and non-invasive administration of systemic analgesics will once again lead to a shift towards monoanalgesic therapy, compared to multimodal methods. Searching for high-risk patients with regards to insufficient analgesia during standard procedures by testing the threshold for thermic pain or using genetic testing is further down the road. Even in acute postoperative pain management we may use a paraphrase of Occam's razor: "Use the simplest things that work well," or a statement by Albert Einstein: "Everything should be kept as simple as possible, but not simpler."

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Appendix 1

POSTOPERATIVE ANALGESIA PROTOCOL

Name _____ **Type of analgesia** epidural ☐
Birth Cert. No. _____ peripheral block ☐
Health Insurance _____ intravenous ☐
Department _____ **Estimated termination on** _____
Surgical procedure _____
Analgesia initiated on _____ next dose: _____ continuous ☐
Initial bolus _____ bolus ☐

Syringe pump contents

Number	Date	Time of start	Type of LA	LA -- mL:	saline mL:	Other adjuvants	Signature
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							

Postoperative pain and its management, patient's condition

time	date																							
	hour	3	6	9	12	15	18	21	24	3	6	9	12	15	18	21	24	3	6	9	12	15	18	21	24
VAS																									
verbal assessment																									
activity																									
sedation																									
analgesia	mL/h																								
	bolus																								
„rescue"																									
medication	drug																								
	dosage																								
SpO_2																									
complications																									

VAS pain assessment – using a VAS ruler [1–10], if sleeping, do not wake the patient up →S
/– VAS and verbal assessment of pain – **before/after** therapeutic intervention
VAS over 4 and verbal assessment over 3 must be treated

Assessment of the level of sedation:
1. awake
2. drowsy
3. asleep, responds to verbal stimuli
4. asleep, responds to pain
5. unresponsive

Activity
C calmness
M movement

Verbal assessment of pain:
1. none
2. almost none
3. mild
4. annoying
5. excruciating

Complications:
1. nausea
2. vomiting
3. itching
4. headache
5. urinary retention
6. obstipation
7. other.....

Appendix 2

Excerpt from the guidelines for the treatment of acute pain at Na Homolce Hospital (published with the consent of the hospital).

Part 1 Material provision of acute pain management

Art. 1

Pain medication

(1) When using pain medications, the hospital lays emphasis on their combinations and the benefits of their complementary effects (multimodal analgesia).
(2) Record in the medication chart for analgesics administered at fixed intervals must include:
a) name of the drug,
b) size of a single dose,
c) time of administration,
d) interval between doses,
e) maximum daily dose.
(3) Record in the medication chart for analgesics administered according to the level of pain and individual needs of the patient must include:
a) name of the drug,
b) size of a single dose,
c) minimum interval between doses,
d) target VAS score, until which the analgesic is administered.

Art. 2

Medication for the treatment of side effects

(1) Medication for the treatment of side effects includes:
a) antiemetics,
b) medication for the treatment of opioid overdose (naloxone); each ward where opioid analgesics are administered must keep a minimum amount of naloxone
c) medication for the treatment of opioid-induced itching
d) medication for the treatment of paralytic ileus
e) medication for the treatment of urinary retention
f) medication for the treatment of qualitative disorders of consciousness,
(2) Specific recommendations for the treatment of complications associated with acute pain management are included in the annex to these guidelines.

Art. 3

Tools

Pain management tools include:
a) tools for measuring vital signs,
b) tools for treating the patient in case of impaired vital signs
c) tools for the administration of oxygen therapy,
d) tools for the administration of advanced analgesic techniques.

Part 2 Staffing, powers and functions of the medical personnel involved in acute pain management

Art. 1

Acute pain service team

(1) An acute pain service team consists of an APS nurse and an APS physician, who is a member of the department of anesthesiology and intensive care
(2) The availability of the APS service is specified in the operating rules of the department of anesthesiology and intensive care.
(3) Personnel involved in acute pain management:
a) APS nurse
b) APS physician,
c) anesthesiologist administering anesthesia, d) bedside nurse,
e) attending physician.

Art. 2

APS nurse

The APS nurse is obliged to:
a) monitor the quality, safety, and effectiveness of acute pain management, prevention and treatment of adverse effects and complications associated with acute pain management, in cooperation with the anesthesiologist, attending physician, and nursing staff,
b) check whether acute pain and adverse effects associated with its treatment are monitored and treated according to the established recommendations and guidelines,
c) check the records in the patient's charts,
d) record pain management rounds into the patient's charts,
e) supervise acute pain management and patient care in the immediate postoperative period,
f) perform audits and studies on acute pain management,
g) perform daily rounds at the bedside of patients after surgery with a focus on acute pain management and the prevention and treatment of the associated adverse effects,
h) perform the requested rounds in patients with acute pain,
i) cooperate with nursing staff in monitoring acute pain and oversee the quality of this monitoring,

j) consult acute pain management and the associated adverse effects, recommend procedures within the adopted guidelines, and if the treatment fails, consult an anesthesiologist or attending physician, or both.
k) assist the nursing staff with orientation in the issue of acute pain management, participate in the education for the nursing staff, physicians, and patients,
l) assist and supervise the use of advanced techniques of acute pain management (patient-controlled analgesia, epidural analgesia, other types of regional analgesia),
m) check the condition of the tools used for advanced techniques of acute pain management in cooperation with the nursing staff and an anesthesiologist.

Art. 3

APS physician

The APS physician is obliged to:
a) establish, adjust, assess, and check the system of acute pain management in the hospital, in cooperation with other anesthesiologists and surgeons and in cooperation with an APS nurse; supervision of acute pain management falls under the department of anesthesiology and intensive care,
b) in cooperation with an APS nurse participate in the rounds in patients with acute pain, oversee the prescribed analgesia, and adjust it in accordance with the adopted guidelines and recommendations if necessary; if the treatment under these guidelines and recommendations fails, then upon the request of the surgical department staff modify the treatment beyond the agreed guidelines and recommendations,
c) provide consultation in patients with difficult-to-manage acute pain,
d) plan perioperative and postoperative pain management in specific patient populations, in cooperation with a specialist on chronic pain management,
e) design audits and studies on acute pain management,
f) comment on the material and medical equipment of the hospital related to acute pain management and treatment of the associated adverse effects.

Art. 4

Anesthesiologist

(1) Within the preoperative examination, the anesthesiologist administering anesthesia is obliged to educate the patient on postoperative pain, its monitoring, and the plan for its treatment with respect to the surgical procedure, age, comorbidities, and the patient's capacity to understand.
(2) The anesthesiologist is obliged to:
a) select a suitable procedure for perioperative and postoperative pain management,
b) administer anesthesia with adequate analgesia; the patient must not have pain score above 3 out of 10 (tolerable) when being transferred from the operating/PACU room to a ward,
c) in accordance with the recommendations, prescribe postoperative analgesia and prevention or treatment of the associated adverse effects and monitoring necessary for safe postoperative course in the immediate postoperative period,
d) hand over information on the patient to the department nurse according to the established rules,

e) check that the patient to be transferred to the ward is provided for according to the established rules,
f) at the end of the surgical program visit patients, whom s/he had anesthetized,
g) be educated on acute pain management,
h) be familiar with hospital regulations on acute pain management and other related procedures.

Art. 5

Bedside nurse

(1) The bedside nurse is obliged to:
a) monitor
1. pain according to the adopted guidelines (VAS, or objective signs of pain)
2. vital functions according to the adopted guidelines,
3. incidence of potential complications associated with acute pain management,
b) record the information in the patient's documentation,
c) administer medication for the treatment of pain and any complications associated with pain management according to the prescription,
d) together with an APS nurse evaluate:
1. success of pain management in a particular patient,
2. incidence of adverse effects, technical failures, and other events associated with acute pain management,
e) if the treatment of acute pain is insufficient, contact the attending physician or an APS nurse,
f) if necessary, inform the patient about pain treatment options,
g) be educated on acute pain management (workshops at the department led by an APS nurse or physician, on-the-job training in cooperation with an APS nurse or physician).

Art. 6

Attending physician

In accordance with the established recommendations and guidelines, the attending physician is obliged to:
a) adjust and prescribe analgesia for the individual patients,
b) prescribe or modify the prescription for the treatment of complications associated with acute pain management,
c) check the monitoring of acute pain and vital signs,
d) in cooperation with an APS nurse, physician, or bedside nurse, address any complications and unusual situations that might occur in connection with acute pain management,
e) be educated on acute pain management (workshops at the department led by an APS nurse or physician, on-the-job training in cooperation with an APS nurse or physician).
f) be familiar with hospital regulations on acute pain management and other related procedures.

Part 3 Rules of communication

Art.1

Communication anesthesiologist – patient

(1) Within the preoperative anesthesiological assessment, the anesthesiologist is obliged to properly educate the patient about potential postoperative pain, treatment options, and potential complications that might arise from the treatment of pain.
(2) The anesthesiologist is obliged to inform the patient about the principles and methods of monitoring postoperative pain.
(3) The anesthesiologist performs the instruction as soon as the patient's condition allows and takes into account the patient's current capacity to understand.

Art. 2

Communication nursing staff – patient

In accordance with the adopted guidelines, the patient is asked about the intensity of pain. The nursing staff helps the patient express the intensity of pain and participates in patient education.

Art. 3

Communication anesthesiologist – attending physician (surgeon)

(1) The surgeon informs the anesthesiologist about the extent and potential painfulness of the surgical procedure. The anesthesiologist informs the surgeon about the planned type of anesthesia technique and about the plan for postoperative pain management.
(2) The anesthesiologist prescribes the treatment of postoperative pain for the immediate postoperative period after consultation with the surgeon and in accordance with the established guidelines and recommendations.
(3) The surgeon observes general recommendations on pain management and modifies the treatment in line with these recommendations, should the initial prescription be insufficient.

Art. 4

Communication APS team member – nursing staff at the department

(1) Initially, an APS team member assists the nursing staff with acute pain management and with the treatment of any associated complications.
(2) The nursing staff together with an APS team member regularly visit patients with acute pain, patients being treated for acute pain, and patients using advanced techniques for acute pain management.
(3) An APS physician may change the analgesic and any related treatment in the medication sheet. In this case, the APS physician informs the attending physician about any changes and reasons for them.
(4) An APS nurse informs nurses and the attending physician about any potential errors in the prescription for acute pain treatment (dosage, intervals, procedures).
(5) Within the specified hours, the nursing staff can contact an APS nurse or physician for consultation; outside these hours, they can contact the anesthesiologist on duty.

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