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REVIEW ARTICLE

Pharmacological management of postoperative pain

Katarina Savić Vujović[1], Sonja Vučković[1], Branislava Medić[1], Dragana Srebro[1], Ana Jotić[2]

[1]University of Belgrade, Faculty of Medicine, Department of Pharmacology, Clinical Pharmacology and Toxicology, Belgrade, Serbia

[2]Clinic for Otorhinolaryngology and Maxillofacial Surgery, University Clinical Center of Serbia, Belgrade, Serbia

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Correspondence to:
Katarina Savić Vujović

Department of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade

1, Dr Subotića Street, 11000 Belgrade, Serbia

E-mail: katarinasavicvujovic@gmail.com; katarina.savic-vujovic@med.bg.ac.rs

Summary

Postoperative pain is a widespread and underestimated problem both in Serbia and globally. Numerous studies conducted in countries with advanced healthcare systems have shown that even in the 21st century, postoperative pain is not adequately managed. More than 80% of patients undergoing surgical procedures experience acute postoperative pain, with 75% describing it as moderate, severe, or extreme. Postoperative recovery depends on patient characteristics and factors that facilitate postoperative recovery, including the presence or absence of postoperative complications. The pharmacology of postoperative pain targets pathophysiological mechanisms such as nociception, peripheral sensitization, ectopic activity, and central sensitization. Modern pharmacological management of postoperative pain involves balanced multimodal analgesia. The principle of multimodal analgesia is based on the multifactorial nature and complexity of pain transmission pathways and is defined as the use of various medications or techniques with different mechanisms of action on the peripheral or central nervous system, which can have additive or synergistic effects. Several drug groups are involved in the multimodal approach, each with a specific pathophysiological mechanism of action. The effectiveness of opioid analgesics in treating moderate to severe postoperative pain is achieved due to the lack of a ceiling effect. However, increasing dosage leads to increased side effects. Nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 inhibitors (COX-2), and systemic steroids reduce the inflammatory component of surgical pain. Systemic and local anesthetics reduce the release of inflammatory mediators, interleukin-(IL-6, IL-1β, and IL-1 receptor antagonist (-1RA)). Gabapentinoids bind to the α-2-δ-1 subunit of voltage-gated Ca^{2+} channels in the central nervous system (CNS), reducing the release of key excitatory neurotransmitters involved in nociception. α-2-agonists, such as clonidine and dexmedetomidine, modulate pain impulse transmission by activating the spinal cord's presynaptic and postsynaptic α2 receptors. Local anesthetics (e.g. lidocaine) block neural transmission by inhibiting voltage-gated Na^{+} channels, thus preventing the transmission of pain stimuli from the periphery to the central nervous system. N-methyl-D-aspartate receptor (NMDA receptor) antagonists, ketamine and magnesium, reduce central sensitization mechanisms.

Keywords: postoperative pain, pharmacological management, drugs

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INTRODUCTION

Pain, respiration, temperature, pulse, and blood pressure are the five essential vital signs. Pain is the most common symptom in clinical practice leading patients to seek medical attention. In patients suffering from prolonged intense pain, there is a reduced ability to function normally and a decrease in work capacity (1).

Postoperative pain remains a widespread and still underestimated problem both in Serbia and globally. Numerous studies conducted in countries with developed healthcare systems have shown that even in the 21st century, postoperative pain is not adequately managed despite advancements in pain therapy. After surgical intervention, a significant number of patients experience moderate to severe postoperative pain (2, 3). More than 80% of patients undergoing surgical procedures experience acute postoperative pain, with 75% of these patients describing the pain as moderate, severe, or extreme (4). Approximately 30-40% of patients experience inadequately managed postoperative pain. There are differences in pain perception among different populations due to varying genetics, social, and cultural factors.

Postoperative pain is a specific entity. Although inflammation and nerve tissue damage occur, the pathophysiology of postoperative pain is unique, and its consequences are specific. Both acute and inadequately managed postoperative pain are not only unpleasant experiences but also trigger a stress response, increasing the risk of complications alongside the surgical trauma (5). These processes initiate a cascade of endocrine, immune, and inflammatory responses, and the body experiences increased stress hormone levels, enhanced catabolism, tachycardia, increased myocardial consumption, increased cardiac volume, a tendency towards thromboembolism, vasoconstriction, and reduced gastrointestinal tract mobility. The result of these changes is increased morbidity and mortality (6). Uncontrolled pain can lead to postoperative cognitive dysfunction and may also result in the development of chronic pain. Adequate management of postoperative pain can lead to faster recovery, better outcomes, and shorter hospital stays (7).

PATHOPHYSIOLOGY OF POSTOPERATIVE PAIN

Postoperative recovery depends on patient characteristics and factors that facilitate recovery, including the presence or absence of complications after surgery. At the site of surgical intervention, there is significant tissue trauma, leading to the release of numerous inflammatory mediators: potassium, hydrogen ions, adenosine, prostanoids, bradykinin (BK), histamine (5-HT), nerve growth factors (NGF), cytokines, and chemokines. These inflammatory mediators affect the function of nociceptors (pain receptors) around the trauma (8). Nerves transmit impulses to the dorsal horns of the spinal cord, the first site where these stimuli are processed sensorily from the periphery. Information about the stimulus is then relayed to higher centers in the CNS, where pain acquires a "conscious" component.

Peripheral nerve damage leads to sensitization, characterized by spontaneous nerve activity, a lowered activation threshold for nociceptors, and increased response to stimuli. Nerve damage itself leads to an increased frequency of nociceptor impulse firing, and consequently, an increase in pain intensity (7, 8). Pain manifests at the peripheral level due to a reduced nociceptor threshold and at the central level by heightened excitation of spinal neurons responsible for transmitting pain signals (6-8).

Peripheral sensitization occurs due to nociceptor activation by various stimuli and is characterized by an amplification of signals in peripheral nociceptive neurons. There is a lowered threshold and heightened response of nociceptive neurons at the periphery. Clinically, peripheral sensitization manifests as hyperalgesia and allodynia. Hyperalgesia is a phenomenon characterized by increased sensitivity to pain. This condition occurs after injury and can become a chronic disorder. Allodynia is the experience of pain, usually on the skin, caused by a stimulus that would not normally provoke pain (9).

The increased influx of pain impulses from the periphery to the spinal cord dorsal horns leads to central neuron sensitization. This process amplifies signals in central nociceptive neurons within the spinal cord dorsal horns. The activation of NMDA receptors underlies the phenomenon of central sensitization. After surgical intervention, there is an increased response to normal mechanical stimuli (allodynia) and the development of a zone of secondary hyperalgesia in the tissue around the surgery site. In addition to contributing to acute pain (such as secondary hyperalgesia and wind-up phenomena), central sensitization in response to trauma or surgery can result in pathological chronic pain conditions (10). α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the spinal cord contribute to pain and hyperalgesia following surgery. Other molecules involved in central sensitization after surgery include extracellular signal-regulated kinases (ERK), brain-derived neurotrophic factor (BDNF), tumor necrosis factor-alpha (TNF-α), mitogen-activated protein kinases (MAPKs), monoamine oxidase B (MAO-B), toll-like receptors (TLR), and cyclooxygenase-2 (COX-2) (11). Spinal inhibitory mechanisms can prevent central sensitization after surgery of spinal α-adrenergic receptor, gamma-aminobutyric acid (GABA) receptor activity. Opioids modulate central sensitization in a complex manner (12).

Descending inhibitory pathways also play an important role at the level of the spinal cord, modulating the transmission of pain impulses. The principle of modulation refers to the mechanism by which pain suppression occurs at the dorsal horns of the spinal cord and at high-

er levels in the nervous system. Endogenous substances such as enkephalins (ENK), norepinephrine (NE), and GABA activate opioid, α-adrenergic, and other receptors that inhibit the release of glutamate from primary afferent nociceptors, blocking the postsynaptic response of second-order neurons. All these pathophysiological mechanisms can be targets for a multimodal approach to minimize the impact of biological processes associated with pain (13).

The pharmacology of postoperative pain is directed towards pathophysiological mechanisms such as nociception, peripheral sensitization, ectopic activity, central sensitization, reduced inhibition, and others.

MEASUREMENT OF POSTOPERATIVE PAIN

In clinical practice, for the simple assessment of acute pain intensity in conscious and verbally communicative patients, unidimensional scales and questionnaires are used. Commonly used scales for assessing postoperative pain are the numeric scale, the verbal scale, the visual-analog scale, and the facial expression scale, which is suitable for children and individuals with limited communication (Wong-Baker faces pain rating scale).

Unidimensional scales are based on self-assessment of pain. They are simple, effective, and minimally burdensome for the respondent (14), and are as follows:

- Numeric rating scale (NRS). This scale consists of ten intervals marked with Arabic numerals from 0 to 10: 0 means no pain; 1-3 indicates mild pain (slightly affects daily activities); 4-6 represents moderate pain (significantly affects daily activities); and 7-10 denotes severe pain (prevents daily activities) **(Figure 1a)**. The therapeutic goal is to achieve values between 0 and 4.
- Verbal rating scales (VRS). These scales allow the patient to describe the intensity of pain using visual and verbal descriptors. Commonly used categories include: no pain, mild pain, moderate pain, and severe pain **(Figure 1b)**.
- Visual analog scale (VAS).VAS is one of the most frequently used tools for measuring pain **(Figure 1c)**. It consists of a 10 cm line, one end labeled "no pain", and the other labeled "the worst possible pain" indicating maximum pain. The patient is asked to mark a point on the line that corresponds to their subjective pain intensity by drawing a vertical line.
- Facial expression scale (Wong-Baker faces pain rating scale). This scale is used for children and individuals with limited verbal communication abilities. It features a series of facial expressions arranged in a gradation of pain intensity. Each facial expression corresponds to a numerical value, allowing the patient to indicate their pain level by selecting the face that best represents their experience **(Figure 1d)** (16).

MULTIDIMENSIONAL PAIN ASSESSMENT

Multidimensional pain assessment involves using a variety of instruments to capture different aspects of pain as follows:

- Brief pain inventory. This questionnaire examines pain and the subjective impact of pain on daily life activities and functional ability (17).
- McGill pain questionnaire. This tool allows for the ranking of multiple dimensions of the subjective pain experience, including sensory, affective, and evaluative aspects (18).
- Neuropathic pain scale. This scale assesses eight qualities of neuropathic pain (sharp, dull, burning, cold,

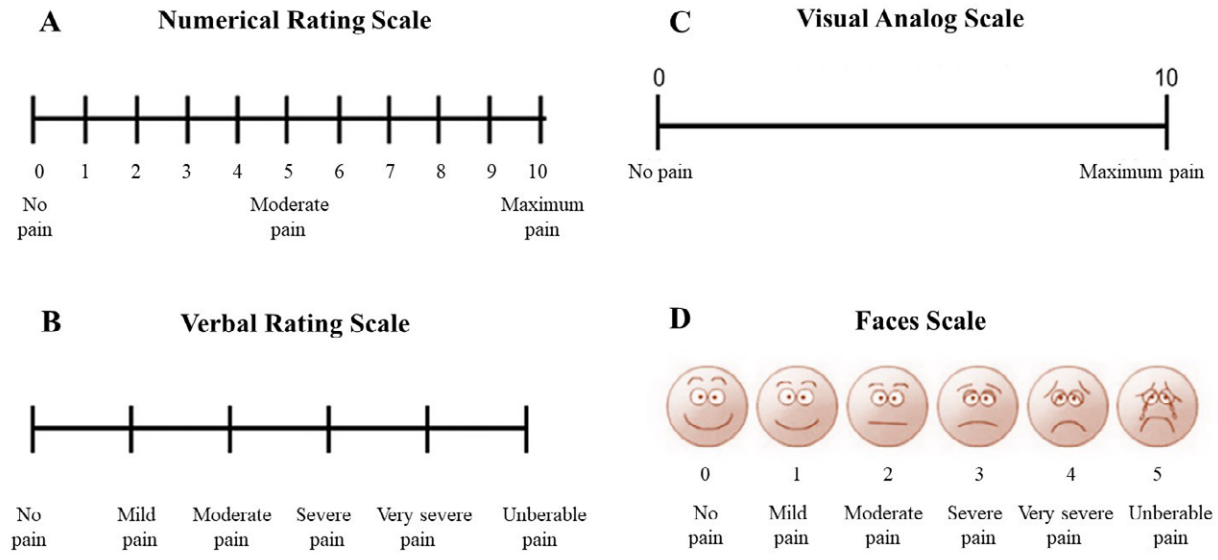

Figure 1. Unidimensional scales for measurement of postoperative pain

sensitive, itchy, deep, superficial) and grades each quality with values ranging from 0 to 10 (19, 20, 21, 22).

MULTIMODAL ANALGESIA

Postoperative analgesia aims to reduce pain intensity and improve functional activity. Modern pharmacological treatment of postoperative pain involves balanced multimodal analgesia. The principle of multimodal analgesia is based on the multifactorial nature and complexity of pain pathways. It is defined as the use of various medications or techniques with different mechanisms of action on the peripheral or central nervous system, which can have additive or synergistic effects (23). The goal of balanced analgesia is to optimize pain relief while minimizing side effects. The choice of analgesics should be tailored to the surgical procedure, as the effectiveness of different analgesics varies with different types of surgery. Multimodal analgesia encompasses both systemic drug administration and regional and neuroaxial techniques. Ideally, multimodal strategies should be initiated during the intraoperative period and continued postoperatively (23).

Opioid analgesics have long been used as a standard for treating postoperative pain (24). The efficacy of opioid analgesics for moderate to severe postoperative pain is due to the absence of a plateau effect. However, increasing the dose leads to increased side effects. Given the pathophysiology of postoperative pain, using only opioid analgesics is not justified. Systemic opioids block nociception through mu, delta, kappa receptors, and central and peripheral G receptors. They have side effects such as respiratory depression and postoperative ileus, which occur through mu-opioid receptors in the medulla oblongata and the gastrointestinal tract and can also cause nausea and vomiting through receptors in the chemoreceptor trigger zone. These side effects delay patient recovery by postponing gastrointestinal function recovery and early feeding (25). ERAS (enhanced recovery after surgery) protocols emphasize the key recommendation to avoid opioids and use a multimodal strategy (26). Multimodal analgesia also includes preventive analgesia, or administering medications to reduce pain before, during, and after surgery. Randomized studies have shown that multimodal analgesia is associated with better pain control and reduced opioid use compared to the use of a single drug (27, 28).

Several classes of medications are involved in the multimodal approach, each with a specific pathophysiological mechanism of action. Non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, and systemic steroids reduce the inflammatory component of surgical pain. Systemic and local anesthetics reduce excessive release of inflammatory mediators (IL-6, IL-1β, and IL-1RA) by decreasing the upregulation of inflammatory cells. Gabapentinoids, by binding to the α-2-delta-1 subunit of voltage-gated Ca^{2+} channels in the CNS, reduce the release of key excitatory neurotransmitters involved in nociception and play a crucial role in neuropathic pain therapy. α-2 agonists, such as clonidine and dexmedetomidine, modulate pain impulse transmission in the spinal cord by activating presynaptic and postsynaptic α2 receptors. Local anesthetics (e.g., lidocaine) block neural transmission by inhibiting voltage-gated Na^{+} channels, thus preventing pain stimulus transmission from the periphery to the central nervous system. NMDA antagonists, such as ketamine and magnesium, reduce the mechanism of central sensitization (29-31).

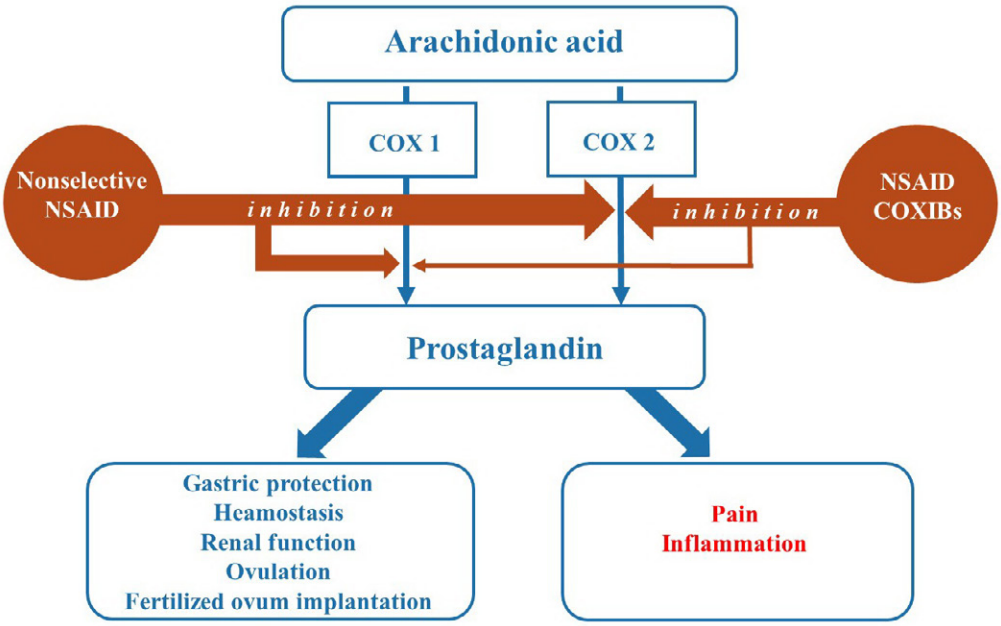

Figure 2. The mechanism of analgesic action of NSAIDs

NSAIDS

NSAIDs are medications used for the treatment of mild to moderate pain. They are not effective for the most severe pain. The mechanism of analgesic action of NSAIDs involves the inhibition of prostaglandin (PG) synthesis both peripherally and in the CNS (32) **(Figure 2)**. NSAIDs inhibit COX enzyme, which metabolizes arachidonic acid into PG and thromboxane (TXA2). There are two COX isozymes, COX-1 and COX-2 (33). NSAIDs can be non-selective inhibitors of both COX-1 and COX-2 or selective inhibitors of COX-2 (coxibs).

In addition to their primary mechanism of action through COX inhibition, non-opioid analgesics activate other mechanisms. They interact with endocannabinoids, NO, serotonergic, noradrenergic, and cholinergic systems (34). NSAIDs also affect ion channels (voltage-gated Na+ channels, voltage-gated L-type Ca2+ channels, voltage-gated and ligand-gated K+ channels, TRP ion channels, etc.), which can contribute to both their analgesic and adverse effects (35-37).

NSAIDs can have significant side effects on the gastrointestinal, cardiovascular systems, and kidneys. They may also prolong bleeding time and exacerbate bronchial asthma. Coxibs, a subset of NSAIDs, generally have fewer gastrointestinal side effects compared to non-selective COX inhibitors and do not inhibit platelet aggregation (32). Additionally, coxibs are considered safer for patients with aspirin-induced asthma. **Table 1** lists NSAIDs used orally for postoperative pain management.

Table 1. NSAIDs used orally for postoperative pain management.

Drug	Maximum dose	Dosing interval
Ibuprofen	2400 mg/24 h	4-6 h
Naproxen	1500 mg/24 h	6-8 h
Ketoprofen	300 mg/24 h	6-8 h
Indomethacin	200 mg/24 h	8-12h
Ketorolac	300 mg/24 h	6-8 h
Diclofenac	150 mg/24h	8-12h
Celecoxib	200 mg/24 h	24 h
Meloxicam	15 mg/24h	24h
Metamizole-sodium	4g/24h	6h

Legend: The most common NSAIDs with maximum doses and dosing interval used orally for postoperative pain management

PARACETAMOL

Paracetamol is an analgesic used for the treatment of mild to moderate pain. Its analgesic effect is primarily due to COX-1 and COX-2 inhibition both peripherally and centrally. Its analgesic effects are also mediated through activation of the descending pain modulation pathways, including serotonergic, endocannabinoid, and opioid systems (38). Central analgesic effects of paracetamol involve various mechanisms, particularly through the production of the bioactive metabolite AM404 in the central nervous system (CNS). AM404 significantly activates the TRPV1 receptor, which plays a crucial role in how neurons respond to pain within the brain and the dorsal horn. In the periaqueductal gray, AM404 triggers a signaling pathway that includes the TRPV1 channel, mGlu5 receptor, PLC, DAGL, and CB1 receptor (39). Paracetamol has weak anti-inflammatory properties.

Paracetamol does not cause serious adverse effects on the gastrointestinal tract or the cardiovascular system, it does not inhibit platelet aggregation and does not worsen bronchial asthma. The maximum recommended dose of paracetamol is 4 g per day for adults and 65 mg/kg daily for children. For elderly patients and individuals with existing liver function impairment, a daily dose exceeding 2 g is not recommended. Overdose of paracetamol can lead to severe liver damage. Toxic doses are 7.5-10 g per day for 1-2 days in adults, and 150 mg/kg in children (40). Antidotes for paracetamol poisoning include acetylcysteine and methionine. Prolonged use of high doses of paracetamol can also have toxic effects on the kidneys.

Paracetamol reduces the need for opioids after surgery. The use of morphine is decreased 24 h after surgery when opioids are used in combination with paracetamol. Randomized controlled trials (RCTs) have shown that 1 g of paracetamol is effective in managing postoperative pain when combined with 400 mg of ibuprofen, 60 mg of codeine, or 10 mg of oxycodone (41). When given prophylactically, intravenous paracetamol is associated with reduced postoperative nausea and vomiting (42). Paracetamol, when used in combination with other analgesics, can be part of a multimodal approach to postoperative pain management.

OPIOID ANALGESICS

Opioids are used for treating moderate to severe pain, both acute and chronic. When used appropriately for medical purposes, opioids are effective and safe medications. They are employed to manage acute severe pain, moderate to severe malignant pain, moderate to severe chronic organic pain, postoperative pain, and neuropathic pain. Opioids are used before, during, and after anesthesia and can be administered alone in high doses for cardiovascular surgeries. They work by inhibiting the excitation of nerve endings in the periphery, blocking pain transmission in the spinal cord's dorsal horn, and activating descending pain control pathways.

OPIOID MECHANISM OF ACTION

Opioids exert their analgesic effects by binding to specific receptors (mu, kappa, delta) in the CNS and peripheral tissues. Activation of opioid receptors inhibits presynaptic release and postsynaptic response to excitatory neurotransmitters like glutamate and substance P (32,

43). Additionally, opioids activate descending inhibitory pain pathways by inhibiting inhibitory (GABAergic) interneurons. In inflammatory pain, the activation of mu receptors inhibits the TRPV1 ion channel through G proteins and cAMP. Some opioids, such as fentanyl, tramadol, and buprenorphine, also block voltage-gated Na^+ channels (40). Opioids are highly effective as they act at multiple sites in the pain pathways (presynaptic and postsynaptic regions, various parts of the nervous system).

Opioids can be classified based on origin into natural, semisynthetic, and synthetic types. They are also categorized by potency into strong and weak opioids, and by action into agonists, partial agonists, and antagonists. Additionally, they can be classified based on action speed into fast and slow-acting opioids (44). Commonly used opioids are mu receptor agonists (μ). Morphine and fentanyl are the most well-known and potent analgesics. They have no upper limit of efficacy and can relieve even the most severe pain but are limited by side effects such as respiratory depression. Partial agonists and agonist-antagonists (nalbuphine, pentazocine, and butorphanol) have weaker analgesic effects compared to pure agonists but also cause fewer side effects such as sedation, psychomimetic effects, and dependency.

Tramadol has a unique mechanism of action. It has a weak affinity for μ receptors and inhibits serotonin and norepinephrine reuptake. It causes less respiratory depression and dependence compared to μ receptor agonists. Tapentadol is similar to tramadol but does not inhibit serotonin reuptake, reducing interactions with other serotonergic drugs. It has greater potency and fewer active metabolites compared to tramadol. Tapentadol is used for moderate to severe chronic pain and has 20 times less affinity for μ receptors than morphine but provides three times less analgesic effect.

Opioids have a broad range of side effects, including nausea, vomiting, constipation, dry mouth, bile duct and sphincter spasms, muscle rigidity, hypotension, respiratory depression, bradycardia, tachycardia, palpitations, postural hypotension, hallucinations, dizziness, euphoria, dysphoria, mood changes, dependence, confusion, drowsiness, sleep disorders, headaches, sexual dysfunction, urinary difficulties, ureteral spasms, miosis, vision disturbances, sweating, skin flushing, rash, urticaria, and itching (45, 46). Sudden discontinuation of opioid therapy can lead to signs of physical dependence, so the dosage should be reduced gradually, first by 50-75%, then by about 20% per day (40).

Recent technological innovations in opioid delivery include formulations that provide extended or rapid release of the active substance, infusion systems, and mini pumps for continuous intravenous and intraspinal administration. These technologies help individualization of the treatment and improve tolerability. Intravenous PCA (patient-controlled analgesia) and epidural analgesia, particularly PCEA (patient-controlled epidural analgesia), offer superior postoperative analgesia, reduce complications, and enhance patient recovery. However, there is a significant fear of misuse and "opiophobia" (47).

Table 2. Forms and doses of opioid analgesics in pain therapy

Drug	Dosage formulation/ route of administration	Dose for the pain therapy
Morphine	solution for injection /i.v. ili i.m.	20 mg/ml solution for injection
	oral drops oral solution syrup	20 mg/ml 10 or 30 mg/5ml 10 mg/5ml
Hydromorphone	extended-release tablet	8, 16 i 32 mg once daily
Oxicodone	capsule extended-release tablet oxicodone+naloxone - extended-release tablet	2, 10, 20 mg on 4-6 h 5, 10, 20, 40, 80 mg on 12 h 5+2,5; 10+5; 20+10; 40+20 on 12 h
Petidine/Meperidine	solution for injection 100 mg/2ml	Dose 0,5-1mg/kg (25-50 mg) •Max 600 mg, not longer than 48h
Fentanyl	spray fentanil patch – chronic pain	10-20 μg/kg for children i 400-800 mcg for adults 30 min before pain procedure or for breakthrough pain. 25, 50, 75, 100 μg/h 12, 25, 50, 75,100 μg/h
Buprenorphine	sublingual tablet	2 i 8 mg on 24 h
Codeine	tablet	30 mg na 6h do 60 mg on 4h
Tramadol	solution for injection • extended-release tablet	50, 100 mg 50, 100, 150 mg • Max 400-500 mg/day

Legend: The most common opioid analgesics (forms and doses) in pain therapy.

i.v. – intravenous; i.m. – intramuscular.

Table 3. Patient-Controlled Analgesia (PCA)

Drug	Initial – bolus dose	Rate of continuous infusion	Lockout interval (min)
Morphine	0.5-2.5 mg		
	1-2	5-10	
Fentanyl	10-20 μg		
	-	4-10	
Alfentanyl	0.1-0.2 μg	-	5-8
Sufentanyl	2.5 μg	-	4-10
Metadone	0.5-2.5 mg	-	8-20
Meperidine	5-25 mg	-	5-10
Pentazocine	5-30 mg	-	5-15
Nalbuphine	1-5 mg		5-15
Buprenorphine	0.03-0.1 mg	4-6	8-20

Table 2 shows different forms and doses of opioid analgesics for pain therapy, whereas **Table 3** shows the benefits and applications of infusion PCA and PCEA systems.

LOCAL ANESTHETICS

Local anesthetics (LAs) are adjunctive medications used in pain therapy. They have both analgesic and anti-inflammatory effects. The mechanisms of action for local anesthetics are diverse and include as follows:

- Blocking voltage-gated Na^+ channels. This prevents the propagation of nerve impulses.
- Blocking Ca^{2+} and Na^+ channels. This further inhibits nerve signal transmission.
- Blocking presynaptic muscarinic receptors. This interferes with neurotransmitter release.
- Blocking TRPV1 channels. These channels play a crucial role in developing hyperalgesia after injury and/or inflammation.
- Blocking NMDA receptors. This action helps modulate pain signaling (48).

Through these mechanisms, local anesthetics alleviate pain and hyperalgesia. They reduce inflammation and local sensitization by directly suppressing certain stages of the inflammatory response (e.g., neutrophil activation) and by blocking specific pathways in nerve cells activated during inflammation. Some local anesthetics, such as bupivacaine and tetracaine, block TRPV1 channels, while lidocaine activates them and causes a burning sensation after subcutaneous injection (49).

Local anesthetics can be used alone or as part of a multimodal analgesia approach. Routine use of peripheral nerve blocks and infiltration of wounds with long-acting local anesthetics, in addition to regional and general anesthesia, improves postoperative pain control across a wide range of surgical procedures. When used preoperatively, they reduce the need for analgesics and anesthetics during surgery. They also decrease the incidence of postoperative nausea and vomiting by reducing opioid use. These techniques are the most effective, with analgesia typically lasting only 6-8 h (50).

For epidural regional anesthesia, bupivacaine (0.1-0.2%, 1-2 mg/ml), levobupivacaine (0.1-0.2%, 1-2 mg/ml), and ropivacaine (0.2%, 2 mg/ml) are commonly used. Lidocaine is the most frequently used local anesthetic for infiltration anesthesia, central neuroaxial blocks, and peripheral nerve blocks. In the treatment of localized neuropathic pain (e.g., postherpetic neuralgia, diabetic neuropathy), 5% lidocaine is applied locally in the form of a patch (10 cm × 14 cm) (51). Pharmacokinetic studies have shown that only 3% of lidocaine reaches systemic circulation, making minimal systemic side effects, even lower than those seen with pregabalin use.

GABAPENTINOIDS

Gabapentinoids (gabapentin and pregabalin) are adjunctive medications used in the management of postoperative pain. These drugs are structural analogs of γ-aminobutyric acid (GABA) but do not act via GABA receptors. Instead, they bind to the α2δ1 subunit of presynaptic voltage-gated Ca^{2+} channels and inhibit them. By inhibiting these channels, gabapentinoids reduce the release of excitatory neurotransmitters, which helps block the development of hyperalgesia and central sensitization (52). Additionally, there is evidence suggesting that gabapentinoids exert antinociceptive effects through the activation of noradrenergic inhibitory pathways.

Gabapentinoids are used in the treatment of chronic neuropathic pain (e.g., postherpetic neuralgia, diabetic neuropathy, and spinal cord injury-induced pain), fibromyalgia, epilepsy, and anxiety (pregabalin only). They are increasingly utilized in acute conditions, such as acute neuropathic pain (e.g., burn injuries) and perioperative analgesia (53). In the management of postoperative pain, gabapentinoids are not typically used as monotherapy but are rather added to opioid therapy. This combination enhances opioid analgesia, reduces postoperative nausea and vomiting, and helps prevent opioid tolerance (54).

So far, the doses and duration of treatment for postoperative pain have not been standardized. Pregabalin has a more favorable pharmacological profile compared to gabapentin. Its absorption is dose-independent, it is 2 to 3 times more potent than gabapentin, and it has fewer side effects. However, pregabalin can still lead to confusion, drowsiness, potential respiratory depression when combined with remifentanil, changes in cognitive status, and dependency (55).

α-2 AGONISTS

These are adjunctive analgesics used in pain management. Clonidine and dexmedetomidine are examples of drugs belonging to this category. The mechanism of

action of α-2 agonists inhibits Ca^{2+} channel opening and suppresses neurotransmitter release (56). α-2 adrenergic receptor agonists, when administered intrathecally or epidurally, can be beneficial as adjunctive therapy for postoperative, neuropathic, and cancer pain, providing extended analgesia (57). When combined with local anesthetics, they lead to prolonged block duration.

Clonidine is more commonly used in the treatment of postoperative pain. Dosages for clonidine in epidural analgesia are as follows: premedication at 0.15-0.3 mg orally, intramuscularly, or intravenously can reduce morphine requirements by up to 50%; intrathecally, 0.075 mg is added; and epidurally, 1-2 μg/kg as a single dose or 3 μg/kg/24 h (58). Dexmedetomidine is used less frequently. Its drawbacks include the need for intravenous administration, high cost, and the requirement for cardiovascular monitoring due to its characteristic biphasic response. Specifically, blood pressure changes are dose-dependent due to the activation of presynaptic or postsynaptic α-2 receptors, leading to either vasoconstriction or vasodilation of blood vessels with reflex bradycardia (59). Adverse effects of α-2 agonists include hypotension, bradycardia, sedation, nausea, and vomiting.

NMDA ANTAGONISTS – KETAMINE AND MAGNESIUM

Ketamine

Ketamine is an anesthetic that functions as an analgesic when used in subanesthetic doses (60). Its mechanism of action primarily involves non-competitive antagonism of NMDA receptors. Ketamine exerts analgesic properties through opioid μ and δ receptors, AMPA and GABA receptors, and by blocking K^+, Ca^{2+}, and Na^+ channels. It also inhibits NO synthesis and activates descending inhibitory pathways at the level of the spinal cord by increasing the release of dopamine, serotonin (5-HT), and norepinephrine while inhibiting their reuptake (61).

When administered intraoperatively or postoperatively, either as a bolus or infusion, ketamine statistically significantly reduces postoperative pain scores and opioid consumption (62). Recommended doses include an intravenous bolus of ketamine ranging from 0.1 to 0.5 mg/kg, which can be followed by an infusion of 0.1 to 0.6 mg/kg/h. This infusion may be stopped at the end of the surgery or continued until the third postoperative day (63). Doses exceeding 0.35 mg/kg or infusions for acute pain greater than 1 mg/kg are not recommended without intensive monitoring. The American Pain Society suggests a preoperative bolus of 0.5 mg/kg ketamine, followed by an intraoperative infusion of 10 mcg/kg/min, with or without a postoperative lower dose infusion (64).

A single analgesic dose can quickly (within 5-10 min) and transiently (for 2-3 h) reduce pain and the symptoms of allodynia, hyperalgesia, and the wind-up phenomenon. However, the side effects of ketamine limit its clinical use. The most common side effects include psychotropic effects (such as dysphoria, hallucinations, vivid dreams, disorientation, and confusion), nausea, headaches, diplopia, drowsiness, and dizziness. These effects are dose-dependent, typically resolved quickly upon cessation of the drug, and their frequency decreases with lower doses and/or the addition of benzodiazepines (65). Chronic use of ketamine may lead to hepatotoxicity, uropathy (including cystitis, dysuria, hematuria, and incontinence), and cognitive impairments. Contraindications for ketamine use include poorly controlled cardiovascular diseases, pregnancy, psychosis, hepatic dysfunction, and elevated intraocular or intracranial pressure (66).

Magnesium (Mg)

Mg is the fourth most abundant ion in the human body and plays numerous roles in physiological functions (67). It exerts analgesic effects through several mechanisms, by blocking NMDA receptors, and Ca^{2+} channels, and modulating Na^+ and K^+ channels. After local application, Mg^{2+} ions on the periphery modulate the activity of transient receptor potential (TRP) channels, such as TRPV1, TRPV4, and TRPA1 (68). When combined with ketamine, Mg has antinociceptive effects, partly through the activation of serotonergic, noradrenergic, and GABA-ergic systems (65). Mg enhances the analgesic effects of opioids and prevents opioid-induced hyperalgesia. When used perioperatively, MgSO4 (magnesium sulfate) can reduce the need for general anesthetics and improve postoperative analgesia (69).

Typically, during anesthesia induction, MgSO4 is administered intravenously as a bolus dose of 30-50 mg/kg, followed by a continuous infusion of 6-25 mg/kg/h until the end of the surgery or for 4-24 h after the initial bolus. A bolus dose of Mg without infusion has also proven effective in postoperative analgesia (70). Mg has a high therapeutic index, few side effects, and a favorable cost-to-efficacy ratio. It is a safe medication with no adverse effects at doses up to 28 g administered over 24 h (71, 72).

Author Contributions

The conception or design of the work - KSV; preparing the draft of the manuscript – KSV; SV; BM; DS; AJ; interpretation of revised version of manuscript - KSV.

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MEDIKAMENTOZNA TERAPIJA POSTOPERATIVNOG BOLA

Katarina Savić Vujović[1], Sonja Vučković[1], Branislava Medić[1], Dragana Srebro[1], Ana Jotić[2]

Sažetak

Postoperativni bol je i dalje veoma rasprostranjen i još uvek potcenjen problem kako u našoj zemlji, tako i u svetu. Brojne studije koje su sprovedene u zemljama s razvijenim sistemom zdravstvene zaštite pokazale su da čak ni u 21. veku postoperativni bol nije adekvatno tretiran. Više od 80% pacijenata koji se podvrgavaju hirurškim procedurama iskuse akutni postoperativni bol, a 75% pacijenata opisuje akutni bol kao srednje težak, težak ili ekstreman. Postoperativni oporavak zavisi od karakteristika pacijenta, ali i od faktora koji omogućavaju postoperativni oporavak, odnosno od prisustva ili odsustva komplikacija posle operacije. Farmakologija postoperativnog bola je usmerena prema patofiziološkim mehanizmima kao što su: nocicepcija, periferna senzitizacija, ektopična aktivnost, centralna senzitizacija. Savremeno medikamentno lečenje postoperativnog bola podrazumeva balansiranu multimodalnu analgeziju. Princip multimodalne analgezije je baziran na multifaktorijalnoj prirodi i kompleksnosti puteva prenošenja bola, a definiše se kao upotreba različitih lekova ili tehnika sa različitim mehanizmom dejstva na periferni ili centralni nervni sistem, koji mogu imati aditivan ili sinergistički efekat. Nekoliko grupa lekova je uključeno u multimodalni princip, i svaki od njih ima specifičan patofiziološki mehanizam dejstva. Efikasnost opioidnih analgetika u terapiji umerenog do teškog postoperativnog bola ostvaruje se zbog nedostatka plato efekta. Međutim, povećanjem doze dolazi do povećanja neželjenih efekata. Nesteroidni anti-inflamatorni lekovi (NSAIL), ciklooksigenaza-2 inhibitori (COX-2) i sistemski steroidi smanjuju inflamatornu komponentu hirurškog bola. Sistemski i lokalni anestetici redukuju oslobađanje inflamatornih medijatora (IL-6, Il-1β, i IL-1RA). Gabapentinoidi, vezujući se za alfa-2-delta-1 subjedinicu voltažnih kalcijumskih kanala u centralnom nervnom sistemu, redukuju oslobađanje važnih ekscitatornih neurotransmitera uključenih u nocicepciju. Alfa-2-agonisti, kao što su klonidin i deksmedetomidin, aktiviranjem presinaptičkih i postsinaptičkih α2 receptora u kičmenoj moždini modulišu transmisiju bolnih impulsa. Lokalni anestetici (lidokain) blokiraju neuralnu transmisiju blokirajući natrijumske kanale, pa preveniraju transmisiju bolnih stimulusa sa periferije u centralni nervni sistem. NMDA antagonisti, ketamin i magnezijum, smanjuju mehanizam centralne senzitizacije.

Ključne reči: postoperativni bol, farmakološko lečenje, lekovi

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