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An anesthesiologist's perspective on advancements in perioperative analgesia

Перспектива анестезиолога о новинама на пољу периоперативне аналгезије

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SUMMARY

Introduction Effective perioperative pain management remains a cornerstone of modern anesthesiology, directly influencing patient outcomes, recovery times, and overall satisfaction. This review aims to explore advancements in perioperative analgesia, focusing on updated guidelines, innovative strategies for pain management, and the role of multimodal anesthesia in optimizing outcomes. The paper highlights the anesthesiologist's pivotal role in implementing these strategies while addressing challenges such as opioid overuse and inadequate pain control.

Method A comprehensive literature review was conducted, analyzing recent studies, clinical trials, and guideline updates published over the past decade. The review examines the evolution of multimodal anesthesia, which integrates non-opioid analgesics, regional techniques, and non-pharmacologic interventions to reduce opioid reliance and enhance recovery. Special attention is given to the management of pain in vulnerable populations, including pediatric and geriatric patients, and those with chronic conditions.

Results Findings reveal that adherence to evidence-based guidelines, combined with a multimodal approach, significantly improves pain management and patient outcomes. Recent innovations, including the use of enhanced recovery after surgery (ERAS) protocols, perioperative nerve blocks, and adjunct therapies such as ketamine and gabapentinoids, are reshaping clinical practice. The review also emphasizes the importance of personalized pain management plans and continuous education for anesthesiologists.

Conclusion This paper concludes that the integration of updated guidelines, multimodal strategies, and patient-centric care models is essential for achieving optimal analgesic outcomes. Future research should focus on refining multimodal protocols, exploring novel analgesics, and addressing barriers to implementation in diverse clinical settings.

Keywords: perioperative analgesia; multimodal anesthesia; enhanced recovery after surgery

САЖЕТАК

Увод Ефикасна периоперативна терапија бола остаје основа модерне анестезиологије, директно утиче на исходе оперативног лечења пацијената, време опоравка и укупно задовољство пацијената. Овај преглед литературе има за циљ да истражи новине у периоперативној аналгезији, фокусирајући се на нове смернице и стратегије за терапију бола, као и улогу мултимодалне анестезије у оптимизацији исхода лечења. Битно је истаћи улогу анестезиолога у имплементацији ових стратегија, али и изазове у клиничкој пракси, као што су прекомерена употреба опиоида и неадекватна контрола бола.

Методе Спроведен је свеобухватан преглед литературе, анализирајући недавне студије, клиничка испитивања и ажурирања смерница објављених током протекле деценије. Преглед испитује еволуцију мултимодалне анестезије, која интегрише неопиоидне аналгетике, регионалне технике и нефармаколошке интервенције како би се смањило ослањање на опиоиде и побољшао опоравак. Посебна пажња се посвећује управљању болом у угроженим популацијама, укључујући педијатријске, геријатријске и хроничне пацијенте.

Резултати Истраживања откривају да праћење смерница заснованих на доказима, у комбинацији са мултимодалним приступом, значајно побољшавају терапију бола и исходе оперативног лечења пацијената. Недавне иновације, укључујући спровођење побољшаног опоравка након операције (*ERAS*) протокола, употребу периоперативних нервних блокова и помоћних медикамената као што су кетамин и габапентиноиди, значајно мењају клиничку праксу. Овај преглед литературе наглашава и важност персонализованих планова за терапију бола и спровођења континуиране едукације за анестезиологе.

Закључак Треба нагласити да је интеграција нових смерница, мултимодалних стратегија и модела неге усмерених на пацијента од суштинског значаја за постизање оптималних исхода аналгезије. Будућа истраживања треба да се фокусирају на усавршавање мултимодалних протокола, истраживање нових аналгетика и решавање препрека за имплементацију ових метода у различитим клиничким окружењима.

Кључне речи: периоперативна аналгезија; мултимодална анестезија; побољшан опоравак након операције

INTRODUCTION

Effective perioperative pain management is a critical aspect of modern anesthesia. Poorly controlled pain during and after surgery not only delays recovery but can also lead to short- and long-term complications, including chronic post-surgical pain and opioid dependency [1]. Current clinical practice often relies heavily on opioids as the cornerstone of analgesia, despite the well-documented risks of opioid-related side effects, including respiratory depression, nausea, and the potential for long-term dependency. Pain management remains inconsistent across different healthcare settings, with significant variability in the adoption of multimodal analgesic strategies and adherence to evidence-based guidelines [2].

New guidelines and research emphasize the need for multimodal anesthesia – an approach that combines various analgesic techniques and pharmacologic agents that act synergistically to target different pain pathways and reduce the reliance on any single drug, particularly opioids. Techniques such as regional anesthesia and the use of adjunctive medications (e.g., ketamine, dexmedetomidine, and gabapentinoids) are gaining interest in the last decade. The integration of these strategies into routine clinical practice is still slow, due to lack of training, resource constraints, and variability in institutional protocols [1].

The aim of this review is to address updates to guidelines, novel perioperative pain management strategies, and the role of multimodal anesthesia in optimizing surgery outcomes, as well as improving and enhancing patient-centered care.

METHODS

Literature search was conducted using PubMed, MEDLINE, and Google Scholar database for published articles in the past 30 years (1995–2025). Terms used in the search were

"perioperative analgesia", "Multimodal analgesia", "MMA", "enhanced recovery after surgery", "ERAS", "perioperative pain", "multimodal anesthesia", "anesthesia". Further articles were found through cross-referencing. Only articles that included human studies and were published in English were included in the review. Primary studies (e.g., retrospective studies, prospective studies, observational studies, randomized controlled trials etc.), basic science research, metanalyses, and systematic reviews were included, while case reports were excluded from the review.

Current Challenges in Pain Management

Reliance on opioids as the primary analgesic has contributed to the opioid crisis, indicating a need for safer, multimodal approaches. Perioperative pain management is particularly challenging in special populations, such as elderly patients, pediatric patients, and individuals with significant comorbidities. A change in clinical practice is required, which focuses on individualized, evidence-based strategies that decrease opioid use, but still offer efficient analgesia.

Inadequate perioperative pain control

Perioperative pain control remains inadequate, despite advances in anesthetic techniques and pain management protocols. Many surgical patients continue to experience moderate to severe postoperative pain. Poorly managed pain can lead to immediate postoperative complications, prolonged hospital stays, and even long-term health consequences such as chronic post-surgical pain (CPSP) [3].

Chronic Post-Surgical Pain (CPSP) is defined as pain persisting beyond three months after surgery and affects approximately 10–50% of patients, depending on the surgical procedure [4]. Surgeries with the highest CPSP incidence include thoracotomy, mastectomy, total knee

arthroplasty, hernia repair, and amputation. Risk factors for CPSP include poorly controlled acute pain, repeated surgical trauma, nerve damage, psychological stress, and pre-existing chronic pain conditions. Effective perioperative pain management, particularly through regional anesthesia and multimodal analgesia, can significantly reduce the risk of CPSP [4].

Severe postoperative pain can lead delayed recovery and increased morbidity, including the risk of deep vein thrombosis (DVT), pulmonary embolism, pneumonia, and muscle deconditioning. Inadequate analgesia prolongs hospital stays and increases the likelihood of unplanned readmissions, raising healthcare costs. Poorly controlled pain can impair gastrointestinal function, leading to postoperative ileus, nausea, and vomiting, further delaying recovery [5]. It can also have significant psychological and emotional impact, contributing to postoperative anxiety, depression, and sleep disturbances [6].

Opioid use and Associated Risks

Opioids have traditionally been the cornerstone of perioperative pain management due to their potent analgesic effects. Overreliance on opioids and their widespread use has led to a host of complications, including dependency, addiction, and a growing healthcare burden. Studies indicate that 5–10% of opioid-naïve patients who receive opioids postoperatively develop long-term dependence [7]. A significant proportion of opioid-related deaths stem from prescriptions initially provided for postoperative pain management [8]. Adverse effects of opioids include acute opioid tolerance, iatrogenic withdrawal syndrome, persistent opioid use, chronic pain, and opioid-induced hyperalgesia [9].

MULTIMODAL ANESTHESIA PROTOCOL IN PAIN MANAGEMENT

Pharmacological combinations of analgesics and non-pharmacological therapies and minimize opioid use are the fundamental components of a multimodal anesthesia (MMA) protocol. Adjuvant therapies should be administrated before surgery to optimize intraoperative and postoperative analgesia, to reduce opioid-related adverse effects in the recovery period [10].

Multimodal approach is more focused on non-opioid analgesics (nonsteroidal anti-inflammatories, acetaminophen, gabapentinoids, NMDA antagonists, alpha-2-agonists), regional anesthesia techniques and non-pharmacological strategies to decrease the use of opioids and associated side effects [10]. It may be a more effective as a pain control strategy, decreasing the complications associated with suboptimal pain control, such as pneumonia, DVT, and postoperative cognitive dysfunction. Nevertheless, opioids still have a critical role in acute postoperative pain management especially for procedures where a primary regional, neuraxial, or local infiltration is not possible [11].

Acetaminophen remains the recommended first-line treatment for mild-to-moderate acute pain in general population, especially in vulnerable populations. It can be used in combination with NSAIDs with synergistic effect, which is desirable in multimodal protocols for optimal pain control [12]. There is evidence that acetaminophen achieves analgesic effect through multiple pathways. One mechanism of action is through cyclooxygenase (COX)-dependent inhibitory effect and by the formation of the bioactive AM404 metabolite as a potent activator of TRPV1, a major contributor to neuronal response to pain in the brain and dorsal horn. Acetaminophen also decreases central oxidative stress and prostaglandin release, which effects descending pain inhibitory pathways. The side effects are generally mild and include nausea, headache, stomach pain, and a rash, while the most serious side effect is liver toxicity which does not occur unless taken in large quantities [13].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) reduce pain by reducing the activity of cyclo-oxygenase (or COX) enzymes and inhibiting peripheral prostaglandin synthesis. Non-selective NSAIDs such as ibuprofen, diclofenac and naproxen inhibit both COX-1 and COX-2 enzymes. Selective NSAIDs (COX-2 inhibitors, coxibs) such as celecoxib and etoricoxib selectively inhibit COX-2, which plays a greater role in prostaglandin mediated pain and inflammation [14]. NSAIDs are routinely used in perioperative and postoperative analgesia, as opioid-sparing analgesics, for treatment moderate to severe pain in children and adults. Regarding adverse effects and safety of NSAIDs, most patients are not at any increased risk of developing adverse central, gastrointestinal, renal and respiratory adverse events. The recent introduction of celecoxib, a selective COX-2 inhibitor, has significantly decreased the risk of postoperative gastrointestinal bleeding and anastomotic leak that are traditionally associated with non-selective NSAIDs. Despite their overall favorable safety profile, NSAIDs should be used with caution in patients with non-erosive reflux disease, patients with prior myocardial infarction on antithrombotic therapy, patients with asthma, and patients with a history of renal disease [15].

Gabapentinoids (gabapentin and pregabalin) are antiepileptic agents which can be used as perioperative analgesics. Mechanism of actions involves inhibition of presynaptic calcium-mediated neurotransmitter release through effects on α2δ-1 subunits in the dorsal root ganglia and spinal cord which are upregulated in the event of surgical trauma, resulting in non-distribution excitatory neurotransmitters [16]. Gabapentinoids are effective in gynecologic, breast, orthopedic, and spine surgery, when administered two hours before surgery in smaller doses due to concern for respiratory depression [17].

N-methyl D-aspartate (NMDA) antagonist. Ketamine has been shown to effectively alleviate pain as antagonists of central NMDA receptors. Its effects are dose dependent: at anesthetic

doses it produces dissociative anesthesia, whereas at subanesthetic doses (typically 0.25–0.5 mg/kg bolus followed by 0.1–0.3 mg/kg/h infusion) it exerts strong analgesic and anti-hyperalgesic effect without loss of consciousness [18]. The most common adverse events associated with ketamine/s-ketamine are dissociation, anxiety, nausea, increased blood pressure, and headache. Most side effects are mild, transient, dose dependent, and attenuate with subsequent treatments. When compared to ketamine, use of subanesthetic S-ketamine in multimodal anesthesia protocols is associated with fewer psychomimetic adverse effects, less emergence delirium, and overall better tolerability [19].

Magnesium is a NMDA receptor antagonist, causing central nervous system (CNS) depression through calcium channels. Magnesium has analgesic effect, reduces postoperative pain and opioid consumption in surgical patients and can be successfully used as a part of multimodal perioperative analgesia [20].

Alpha-2 agonists (clonidine, dexmedetomidine) are often used perioperatively to enhance analgesia, stabilize hemodynamics, and reduce opioid consumption [2]. They act as antagonists of presynaptic and postsynaptic α_2-adrenergic receptors in the CNS, leading to inhibition of norepinephrine release, decreased sympathetic outflow, and modulation of spinal and supraspinal nociceptive transmission. This results in sedative, anxiolytic, and analgesic effects, along with an opioid-sparing action valuable in perioperative pain management [11]. Adverse effects are generally dose dependent and include bradycardia, hypotension, sedation, and, less frequently, dry mouth and delayed recovery if overdosed.

Intravenous local anesthetics (lidocaine). These medications are currently not routinely use for perioperative pain control, because of limited evidence available in the literature [13]. There are data that indicate that lidocaine infusions reduce postoperative pain scores, nausea, and vomiting, and accelerate bowel function and reduce opioid consumption after abdominal

surgery [21]. Lidocaine inhibits of sodium channels, G protein-coupled receptors, and N-methyl D-aspartate receptors, leading to suppression of local and systemic inflammation, nociceptive transmission, and central sensitization. Side effects from perioperative intravenous lidocaine infusion include drowsiness and blunted response to tracheal extubation, as well as symptoms commonly associated with local anesthetic systemic toxicity such as tinnitus, perioral numbness, lightheadedness, dizziness, visual changes, and more seriously arrhythmias and seizures [22].

REGIONAL AND LOCAL ANESTHESIA TECHNIQUES

Regional anesthesia includes both neuraxial (spinal and epidural) anesthesia and peripheral nerve blocks. These techniques have resulted in better control of perioperative pain, decreased opioid use and time spent in the post-anesthesia care unit after various surgical procedures [23]. There are evidence that show that application of regional anesthesia can prevent persistent postoperative pain and chronic postsurgical pain in postoperative settings. Regional anesthesia techniques carry a certain risk of complications like nerve injury, bleeding, infection, rebound pain and potential local anesthetic toxicity. In the last decade, use of ultrasound guidance has mostly contributed to wider use and the safety of regional anesthesia, resulting in reducing these complications in clinical settings [24].

Traditionally, bupivacaine was mostly used in regional anesthesia. Levobupivacaine and ropivacaine were developed as isomers with nearly identical effects in onset, quality, and duration of sensory block, but better safety profile comparing to bupivacaine [24]. For better pain management, both proved to be effective in combination with fentanyl [23].

Epidural anesthesia and spinal anesthesia are one of the oldest forms of regional anesthesia. They are often used in thoracic surgery, orthopedic surgery, and obstetrical procedures. The paravertebral block involves the delivery of local anesthetics to the paravertebral space near

the spinal nerves emerging from the intervertebral foramen which is a reliable technique for reducing pain in the immediate postoperative period after breast surgery. Upper limb nerve blocks are employed due to the high incidence of postoperative pain in upper limb surgeries. The transverse abdominis plane block involves application of local anesthetics to the fascial plane between the internal oblique and transverse abdominus muscles and it's used for colorectal surgeries and obstetrical procedures. Quadratus lumborum block involves application of local anesthetic around the quadratus lumborum muscle and covers which is effective for abdominal, obstetric, pelvic, and renal surgeries. Erector spinae block is a fascial plane technique used to treat both acute and chronic pain, with many applications ranging from head and neck, thoracic, abdominal, and lower extremity surgical procedures. These techniques are considered safe, result in excellent perioperative analgesia and decrease use of opioids postoperatively [25].

One major drawback of regional anesthesia is its limited duration of effective analgesia. This depends on the type, volume, centration of applied local anesthetic, and patients' comorbidities, but could result in intense postoperative pain and rebound pain. These effects can be more easily managed for patients in hospital settings, than for those who had one-day surgery which usually require for post-discharge medical attention. As a result of efforts to increase the length of analgesia in pre-existing local anesthetics led to development of new formulations of local anesthetics like EXPAREL liposomal bupivacaine and SABER bupivacaine. These medications have significantly reduced postoperative pain levels up to 72 h, opioid consumption and hospital stay, while increasing the time to first rescue opioid medication use [23].

ROLE OF MULTIMODAL ANESTHESIA PROTOCOL IN ENHANCED RECOVERY AFTER SURGERY (ERAS)

The Enhanced Recovery After Surgery (ERAS) protocols are multimodal perioperative care pathways designed to achieve fast recovery in patients after surgical procedures by defining and maintaining preoperative organ function and minimizing the stress response following surgery. Unlike traditional perioperative management, which often focuses on isolated interventions, ERAS integrates multimodal protocols across various perioperative stages to create multidisciplinary, evidence-based approach designed to improve surgical outcomes, minimize reliance on opioids while enhancing pain control and reduce postoperative complications by optimizing perioperative care [11].

A multi-society consensus statement published in Regional Anesthesia & Pain Medicine establishes seven guiding principles for acute perioperative pain management to help institutions enhance surgical patient care [26]. These principles emphasize the need for preoperative evaluation of medical and psychological conditions, screening for potential substance use disorders, a focus on multimodal analgesia incorporating nonpharmacologic interventions, and the use of validated pain assessment tools to guide and adjust treatment. The consensus highlights that clinicians should conduct a thorough preoperative evaluation, assessing medical and psychological conditions, medication history, chronic pain, substance use disorder, and prior postoperative pain treatment responses to develop a personalized pain management plan [11].

Preoperative Phase in ERAS protocol involves comprehensive preoperative preparation, where multimodal anesthesia plays a vital role in effective perioperative analgesia. Psychological preparation of patients, including cognitive behavioral strategies and anxiety reduction techniques, minimizes the stress response to surgery. Preoperative counseling also addresses

expectations regarding postoperative pain control and early mobilization [24]. Preemptive administration of non-opioid analgesics, such as acetaminophen or NSAIDs, is an essential part of ERAS. Preoperative carbohydrate loading reduces insulin resistance and enhances metabolic recovery, indirectly contributing to improved analgesia and reduced catabolism [24]. Patients at risk of chronic pain or opioid use disorder may receive gabapentinoids or NMDA receptor antagonists as part of a preemptive multimodal approach [16].

The intraoperative phase of ERAS focuses on maintaining hemodynamic stability, minimizing surgical stress, and ensuring effective analgesia while avoiding excessive sedation or opioid burden. Multimodal anesthesia within ERAS emphasizes a balance between analgesia and hemodynamic stability. Planned application of fluid therapy prevents fluid overload, which reduces tissue edema, optimizes oxygen delivery, and enhances postoperative recovery. Maintaining normothermia through warming devices reduces surgical stress and supports hemodynamic stability [26]. A balanced anesthesia approach prioritizes opioid-sparing approach prioritize integration of regional techniques and patient-specific sedation. Total intravenous anesthesia (TIVA) with added dexmedetomidine or lidocaine may improve postoperative pain control while avoiding opioid-related side effects such as nausea and ileus [11]. The use of short-acting anesthetic agents facilitates early emergence and immediate postoperative recovery. Suppressing the surgical stress response using multimodal strategies reduces postoperative catabolism, immune dysfunction, and pain hypersensitivity. Techniques such as regional blocks or neuraxial anesthesia mitigate the neuroendocrine stress response to surgery. Anti-inflammatory agents, such as corticosteroids, further enhance recovery by modulating the surgical inflammatory response [14].

The postoperative phase of ERAS focuses on optimizing analgesia to supports rapid emergence and allow patients to regain consciousness and protective airway reflexes faster. Avoiding

long-acting opioids and benzodiazepines facilitates early extubation, reducing the risk of respiratory complications and postoperative delirium [26]. Multimodal analgesia also minimizes postoperative shivering, nausea, and excessive sedation, improving time spent in post-anesthesia care unit. It facilitates early return of bowel function and early oral intake [10]. Early mobility accelerates muscle recovery, shortens hospital length of stay, and decreases the incidence of postoperative complications such as pneumonia and DVT [11].

FUTURE DIRECTIONS AND IMPLEMENTATION OF MULTIMODAL APPROACHES IN SERBIA

The adoption of multimodal analgesia in perioperative protocols in Serbia faces several clinical challenges, although studies were already published on the subject [27]. One of the primary concerns is the existing training gap among anesthesiologists and surgical teams. Despite the evident benefits of multimodal analgesia, many healthcare professionals lack adequate exposure and hands-on experience in administering regional anesthesia techniques effectively. Additionally, resistance to change among medical practitioners remains a significant obstacle. Many anesthesiologists and surgeons continue to rely on conventional management strategies due to familiarity and institutional inertia. Another critical challenge is the variability in hospital protocols across different healthcare institutions. While some hospitals have adopted comprehensive multimodal analgesia protocols, others continue to follow outdated pain management strategies, leading to inconsistent patient outcomes [28].

Limited access to resources slows down implementation of multimodal analgesia in Serbia. The availability of regional anesthesia techniques and multimodal drug combinations is inconsistent across hospitals, particularly in smaller healthcare facilities. To overcome these challenges, primary goal should be establishing structured educational programs that focus on

multimodal analgesia. These programs should be integrated into anesthesiology training curricula and include hands-on workshops to ensure competency in regional anesthesia techniques. Efforts should be made to promote adherence to national and international guidelines and standardize perioperative pain management protocols across healthcare institutions. Interdisciplinary collaboration between anesthesiologists, surgeons, and pain specialists is essential for the successful adoption of multimodal analgesia. Establishing Acute Pain Service (APS) units in hospitals can also facilitate coordinated pain management efforts and ensure optimal patient care [29].

CONCLUSION

Advancements in perioperative analgesia like importance of multimodal anesthesia, adherence to evolving guidelines, and a personalized approach have significantly transformed pain management and improve patient recovery and satisfaction. By integrating opioid-sparing techniques and regional anesthesia, anesthesiologists can optimize pain control while minimizing adverse effects. Recognizing the variability in patient responses emphasize the need for a personalized approach, where treatment is adapted to factors such as surgical type, comorbidities, and patient preferences. Anesthesiologists and healthcare providers must remain committed to continuous learning and guideline adherence to ensure optimal patient outcomes. Institutional policies should support the widespread implementation of evidence-based analgesic protocols, promoting interdisciplinary collaboration in perioperative care. By prioritizing these efforts, the medical community can continue to advance perioperative analgesia and improving patient safety and quality of life.

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Table 1. Non-opioid analgesics used in multimodal approach of pain control

Analgesics	Analgesic Mechanism of action	Application	Dosage	Adverse effects
Acetaminophen	• Inhibiting COX-1 and COX-2 enyzmes • Activating the TRPV1 and CB-1	Oral, rectal, and intravenous route	• In children > 12 years and adults 500–1000mg every 4-6 hours (maximum 4000 mg daily) • In children one month to 12 years 15 mg/kg per dose every six hours	• Potentiate warfarin anticoagulation • Chronic alcohol misuse increases the risk of toxicity • Contraindicated in cases of active liver disease or severe hepatic impairment. • Other: skin rash, hypersensitivity reactions, nephrotoxicity
NSAIDs	• Non selective inhibition of both COX-1 and COX-2 or selective inhibition of COX-2	Oral, intramuscular, and intravenous route	Diclofenac: 50–75mg mg 2–3 times/daily or (max 150 mg) PO or IM. Ibuprofen: Initial dose 400 mg IV, then 100–200 mg 4–6 hours IV 1200-3200m/daily in 3–4 doses PO Ketrolac: 15–30 mg every 4–6 hours i.m. or i.v. or 10 mg 4–6h PO Meloxicam: 7.5–15 mg daily PO Celecoxib_ 50–200 mg (daily in one or two doses PO	• Prolonged use can lead to gastric, renal and cardiovascular adverse effects • Hepatic adverse effects are less common • Possible hematologic adverse effects in hemophilia, thrombocytopenia, von Willebrand, etc.) • Other: anaphylactoid reactions that involve urticaria and aspirin-exacerbated respiratory disease.
Gabapentinoids	• Inhibition of calcium-mediated neurotransmitter release through effects on α2δ-1 subunits	Oral route	Gabapentine: 900–3600 mg/day in three doses PO Pregabaline:150–600 mg/day in two to three doses PO	• CNS adverse effects (dizziness, senescence, gait disturbances) • Gastrointestinal adverse effects (abdominal distension, abnormal appetite, constipation, dry mouth and nausea) • Weight gain • Respiratory depression when used in combination with opioids
NMDA antagonist (ketamine)	• NMDA and glutamate receptor antagonist	Intranasal, intravenous intramuscular route	• 0.3–0.5 kg/kg IV bolus • 0.1–0.2 mg / kg / h IV infusion • 1 mg/kg intranasally	• Cardiovascular, gastrointestinal, respiratory, neurologic and psychiatric side effects • Coadministration with opioid analgesics, benzodiazepines, CNS depressants, and alcohol, may induce profound sedation, respiratory depression, coma, and potentially fatal outcomes.

				• Coadministration with sympathomimetic medications may increase sympathomimetic effects • Coadministration with theophylline or aminophylline could potentially reduce the seizure threshold. • Contraindicated in patients with aortic dissection, uncontrolled hypertension, myocardial infarction, or aneurysms
Magnesium	•NMDA receptor antagonist	Oral, and intravenous route	• Post-surgery: 30 mg/kg bolus followed by an infusion of 10 mg / kg / hour • Oral intake Children 2.5–5 mg/kg daily Adults 310–420 mg/daily	• Contraindicated in renal dysfunction, pregnancy, and neuromuscular disease. • Hypermagnesemia (levels greater than 2.6 mg/dL and above) can lead to cardiovascular complications, neurological disorder, cardiorespiratory arrest (serum values exceeding 15 mg/dL)
Alpha-2 agonists	• Agonist of presynaptic and postsynaptic α_2-adrenergic receptors nociceptive	Oral, IV, transdermal, epidural, perineural	Clonidine • Oral premed: 2–4 µg/kg; IV bolus: 1–2 µg/kg; • Epidural: 150–300 µg Dexmedetomidine • IV bolus: 0.5–1 µg/kg over 10 min • Infusion: 0.2–0.7 µg/kg/h	• Hypotension, bradycardia, sedation, dry mouth • Contraindicated in severe bradyarrhythmia, hemodynamic instability, severe ventricular dysfunction, uncontrolled cerebrovascular disease
Intravenous lidocaine	• Inhibition of VGSCs • inhibition of G protein-coupled receptors • Inhibition of NMDA receptors	Intravenous route	• 1.5 mg/kg IV bolus • 1–2 mg / kg / h IV infusion	• Cardiovascular (bradycardia, hypotension) and neurological side effects (dizziness, seizures)

COX – cyclooxygenase; TRPV – transient receptor potential vanilloid; CB – cannabinoid; IM – intramuscular; IV – intravenously; PO – per os; NMDA – N-methyl-D-aspartate; CNS – central nervous system; VGSC – voltage-gated sodium channel

