

Multimodal Analgesia for Perioperative Pain Management

Perioperatif Ağrı Yönetiminde Multimodal Analjezi

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Abstract

Postoperative pain is an important problem which is a common condition in patients and can become chronic if left untreated. Ineffective pain management in the postoperative period may increase stress response and may cause vital changes on endocrine, respiratory, cardiovascular, gastrointestinal, and musculoskeletal systems and patient psychology. Side effects from the use of high-dose medication for pain management also increases complications. Multimodal analgesia applications aim to reduce the side effects that may occur with the use of high doses of a single agent by creating additive or synergistic effects by using analgesics with different mechanisms of action together. Therefore, protocols have been developed that aim to minimize complications, eliminate pain, accelerate recovery, encourage early ambulation and thus reduce the length of hospital stay. These include the Enhanced Recovery After Surgery protocols, which include multimodal analgesia and procedure-specific protocols. The aim of this review is to highlight the most optimal patient and procedure-specific perioperative pain management strategies in the light of available evidence.

Keywords: Postoperative pain, multimodal analgesia, ERAS, procedure-specific postoperative pain management

Öz

Postoperatif ağrı, hastalarda yaygın olarak görülen ve tedavi edilmediği takdirde kronikleşebilen önemli bir sorundur. Postoperatif dönemdeki etkisiz ağrı kontrolü, stres cevabı artırır endokrin, solunum, kardiyovasküler, gastrointestinal, kas iskelet sistemleri bozukluklarına ve hasta psikolojisi üzerinde önemli değişikliklere yol açmaktadır. Ağrı kontrolünde yüksek doz ilaç kullanımından kaynaklanan yan etkiler de komplikasyonları artırmaktadır. Multimodal analjezi uygulamaları farklı etki mekanizmalarına sahip analjeziklerin birlikte kullanımıyla additif veya sinerjistik etki oluşturarak, tek ajanın yüksek doz kullanımıyla oluşabilecek yan etkileri azaltmayı amaçlar. Bu bağlamda komplikasyonlarını en aza indirmeyi, ağrıyı ortadan kaldırmayı, iyileşmeyi hızlandırmayı, erken ambulasyona teşvik etmeyi ve böylece hastanede kalış süresini azaltmayı amaçlayan protokoller geliştirilmiştir. Multimodal analjezi uygulamalarını içeren Cerrahi Sonrası Hızlandırılmış İyileşme protokolleri ve prosedür spesifik protokoller bunlardan bazılarıdır. Bu derlemenin amacı mevcut kanıtlar ışığında hasta ve prosedür spesifik olarak en optimal perioperatif ağrı yönetimi stratejilerini vurgulamaktır.

Anahtar Kelimeler: Postoperatif ağrı, multimodal analjezi, ERAS, prosedür spesifik postoperatif ağrı yönetimi

Introduction

Definition and Mechanism of Pain

The International Association for the Study of Pain defines pain as "the sensory and emotional experience associated with actual or potential tissue damage or a similar unpleasant

condition". According to the World Health Organization, it can be classified according to anatomical, etiological, pathophysiological characteristics or duration. To perceive pain, some complex physiological events occur, these events together are called nociception and consist of four stages: transduction, transmission, modulation and perception (Figure 1).

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Transduction is the conversion of a nociceptive stimulus into an electrical signal at sensory nerve endings. Transmission involves the transport of the nociceptive impulse from the peripherals to the center through the nervous system. Modulation is the alteration of nociceptive information by endogenous mechanisms; amplifying, reducing, or blocking the initial signal. Perception reflects the effects of the nociceptive information on the psychological state, the emotional and physical experience of pain shaped by previous pain experiences.

Acute Postoperative Pain

Acute postoperative pain is a type of pain that develops in a patient who has undergone surgery as a result of previous illness, surgical intervention or both. If adequate analgesia is not provided, 10-15% of acute postoperative pain can turn into chronic pain (1). There are some predisposing factors for the development of chronic pain. These factors include young age, female gender, smoking history, depression, anxiety, sleeping disorders, negative affect, presence of preoperative pain, preoperative analgesic use and type/duration of surgery. Although it varies according to the type of surgery, it can turn into chronic pain in up to 80% after amputation surgery and up to 60% after mastectomy and inguinal hernia operations. In addition, a range of pathophysiologic responses involving various systems develop with acute pain in the postoperative

period. In the cardiovascular system, tachycardia, hypertension, increased myocardial oxygen consumption, increased risk of myocardial infarction, deep vein thrombosis may be seen. Decreased motility in the gastrointestinal system and urinary retention may be observed. Musculoskeletal spasms and immobility may be observed. In the neuroendocrine system, catecholamine, cortisol and insulin levels may increase and psychologically anxiety, fear and sleep disturbance may be observed. Especially in patients undergoing thoracic and upper abdominal surgery, inability to excrete secretions, atelectasis, hypoxemia and susceptibility to infection can be seen as a result of inability to use effective respiratory muscles due to pain. Therefore, pain relief is very important in terms of prevention of chronic pain development, reduction of metabolic and stress response, reduction of thromboembolic complications, preservation of cognitive functions, early mobilization and rehabilitation, reduction of hospital stay and cost. Furthermore, it has important effects on the patient outcomes and quality of life (2).

Pain Assessment Scales

When evaluating postoperative pain, the pain characteristics should be questioned in detail and pain intensity should be objectively evaluated with appropriate pain scales. It's important to ask about the characteristics of pain; the onset

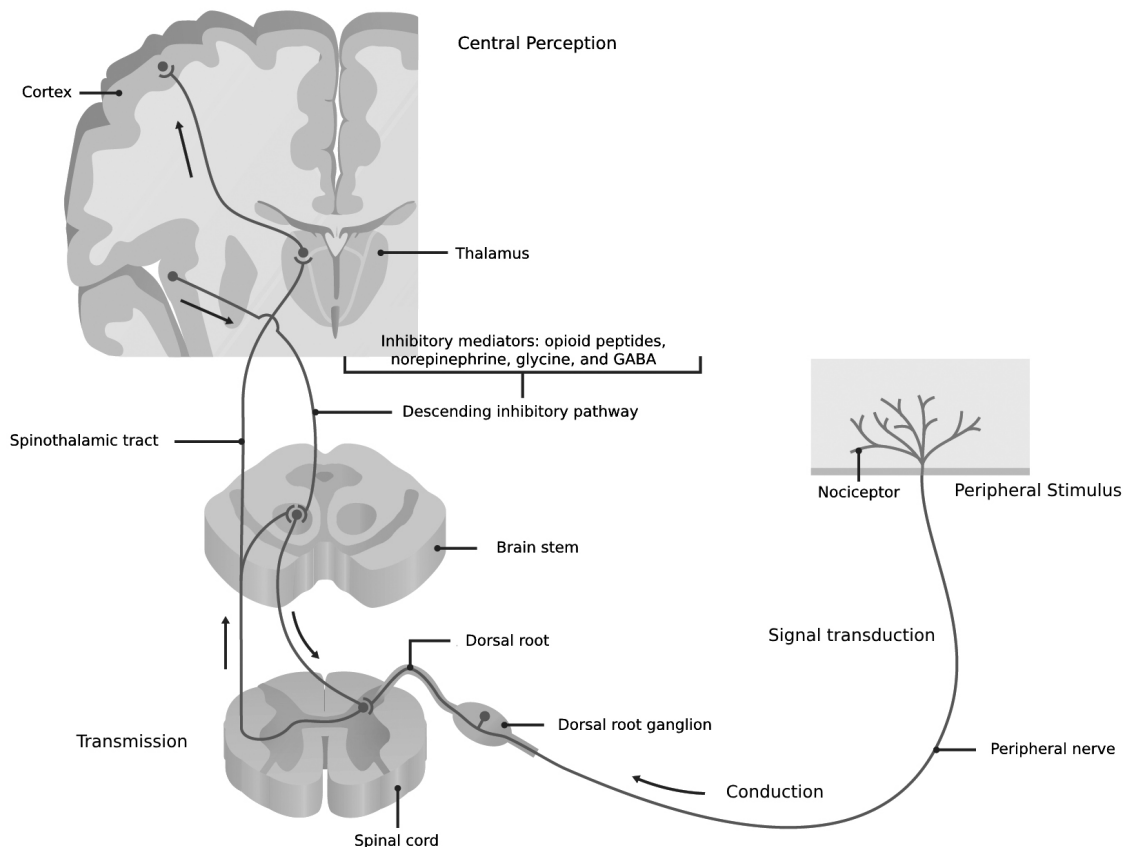


Figure 1: The pain pathway indicating the four processes involved in nociception: transduction, transmission, modulation and perception

pattern, location and radiation, texture, intensity, and duration, pain-relieving or aggravating factors, associated symptoms, and the effectiveness to previous pain treatments are important. Pain scales commonly used to assess the severity of pain include the visual analog scale, the numerical rating scale-11, the verbal pain intensity scale and the FACES scale (which is more suitable for children) (Figure 2).

Postoperative Pain Management and Multimodal Analgesia

Multimodal analgesia is the use of multiple analgesics and adjuvants together that offer pain relief through different mechanisms. When compared to using a single agent, it results in lower doses, better analgesia, reduced opioid requirements and fewer side effects. While an agent is providing peripheral desensitization, the other should provide central desensitization. The combined agents should produce a synergistic or additive effect.

Recent clinical data suggest that a paradoxical response to opioids may develop, that opioid-taking patients may actually become more sensitive to painful stimuli and thus result in hyperalgesia instead of analgesia. This phenomenon, known as opioid-induced hyperalgesia (OIH), is probably caused by up-regulation of the pro-nociceptive pathways within the central and peripheral nervous systems. Although hyperalgesia is traditionally associated with chronic pain, acute OIH may occur after intraoperative or postoperative administration of high doses of potent opioids. As a result, despite an increase in postoperative opioid use, it can cause paradoxically increased postoperative pain (3,4).

When considering the pharmacologic agents used in multimodal analgesia; paracetamol, whilst forming the basis, is the safest and most cost-effective non-opioid analgesic that inhibits central and partially peripheral prostaglandin synthesis.

Non-steroidal anti-inflammatory drugs (NSAIDs) act by inhibiting the cyclo-oxygenase enzyme and prostaglandin synthesis. They provide effective analgesia in mild to moderate pain and can be used as an adjunct to opioids in the treatment of more severe pain. NSAIDs and cyclooxygenase (COX) inhibitors have been shown to have equivalent analgesic efficacy after minor and major surgery. There is evidence to support that COX inhibitors are a better option for perioperative pain management due to reduced GI side effects and lack of antiplatelet activity (5).

Gabapentinoids act by inhibiting voltage-gated calcium channels. They are antiepileptic drugs that are often used as a treatment for chronic and neuropathic pain. There are reports of their use in breast, prostate and vertebral surgery as part of a multimodal analgesia regimen (6). Alpha-2 agonists act by stimulation of alpha-2 receptors in the dorsal horn of the spinal cord and attenuation of nociceptive signals. Alpha-2 agonists have come to the fore especially in bariatric surgery due to decreased opioid consumption and related side effects, although evidence regarding optimal dose regimens and postoperative use is insufficient (7). Ketamine acts by antagonizing N-methyl-D-aspartate (NMDA) receptors in the brain and spinal cord. IV infusions at subanesthetic doses (<1 mg/kg) show anti-hyperalgesic and anti-allodynic effects. It may be preferred in patients with obstructive sleep apnea and opioid tolerance. Tramadol is a weak-acting synthetic opioid that acts through inhibition of serotonin and norepinephrine reuptake and activation of central μ -opioid receptors.

Magnesium acts through inhibition of glutamatergic synapses by upregulation of voltage-dependent Na⁺, K⁺, and Ca²⁺ channels and by blocking NMDA receptors. It can be used in multimodal analgesia regimens at 50 mg/kg bolus doses followed by 8 mg/kg/h infusion (8).

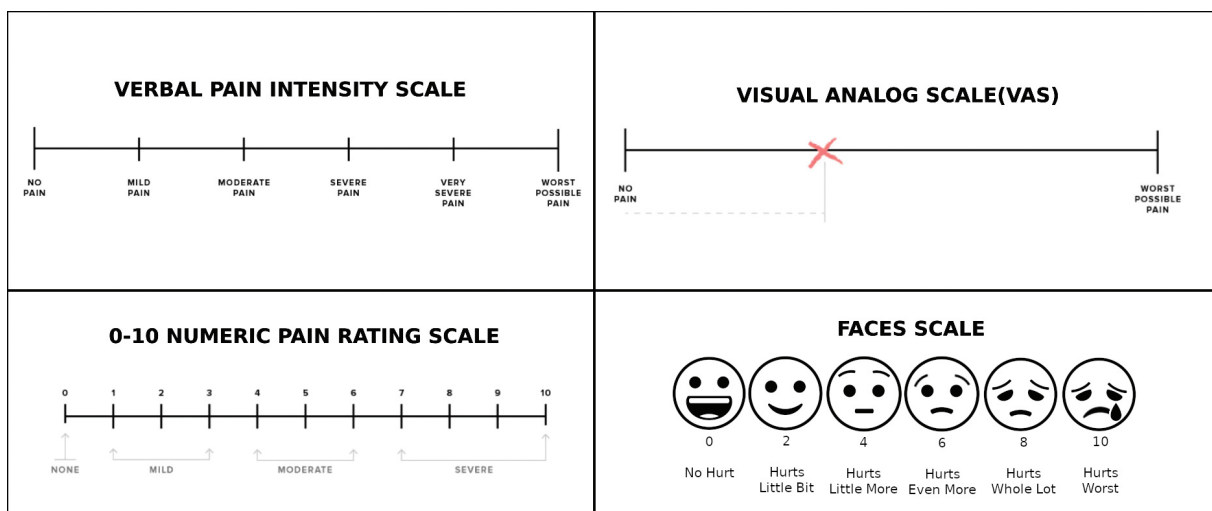


Figure 2: Examples of pain assesment tools

Lidocaine is an amide type local anesthetic with analgesic, anti-inflammatory and anti-hyperalgesic properties. It acts by inhibition of glutamatergic synapses and Na⁺ channel blockade by blocking NMDA receptors. It is available as 1–2 mg/kg IV bolus followed by 1–2 mg/kg/h continuous iv infusion continuing up to 24–48 hours postoperatively. Studies have shown that lidocaine infusions have analgesic efficacy equivalent to epidural analgesia in patients undergoing cytoreductive surgery-hyperthermic intraperitoneal chemotherapy with open abdominal surgery (9).

In addition to these applications, neuraxial blocks, peripheral nerve blocks and wound infiltrations including local anesthetic drug applications are included. Plane blocks such as trans-abdominal plane block, serratus plane block, quadratus lumborum block, erector spinae plane block, pectoral nerve block can be used for thoracic surgery, breast surgery and abdominal surgery. Thoracic epidural analgesia is the gold standard method of analgesia in patients undergoing open colorectal and thoracic surgery. Quadratus lumborum block may be an alternative to epidural analgesia as it provides somatic and visceral analgesia between T4–L4. Spinal analgesia can be administered as an adjunct to general anesthesia in laparoscopic procedures using opioids, local anesthetics or a combination of both agents. Intrathecal opioids act by blocking the transmission of Substance-P.

ERAS and Procedure Specific Postoperative Pain Management

ERAS is a brand of good clinical practices that is used to describe the concept of multimodal perioperative interventions to improve postoperative outcomes. Procedure Specific Postoperative Pain Management (PROSPECT) is an organization with pragmatic recommendations for an evidence-based, procedure-specific pain control methods, covering preoperative, intraoperative and postoperative periods and including implementation recommendations that are compatible with ERAS protocols. The preoperative evaluation of PROSPECT includes assessing preoperative pain, opioid use, previous bad experience, inappropriate expectations of the patient, level of anxiety about the surgical outcome, psychological status, and functional pain status. It then includes patient preparation, education, information and control of current pain. Recommendations are based on many evidence-based studies specific to different surgeries.

PROSPECT recommendations for some of the common surgical practices are listed as follows; craniotomy includes preoperative and intraoperative paracetamol, non-steroidal anti-inflammatory agents, scalp block, incision site infiltration and IV dexmedetomidine infusion. In the postoperative period, paracetamol, non-steroidal anti-inflammatory agents and opioids as rescue analgesics are available. Gabapentinoids, IV

magnesium, and IV lidocaine infusions are not recommended due to lack of sufficient studies (10).

Sternotomy includes preoperative and intraoperative paracetamol, NSAIDs, dexmedetomidine and magnesium infusion as an adjunct especially when basic analgesics are not available, parasternal block or surgical wound infiltration. Non-pharmacologic therapies such as music and massage are also recommended in addition to pharmacologic treatment. Postoperative paracetamol, NSAIDs and opioids as rescue analgesics are available. Non-recommended applications include COX inhibitors, gabapentinoids, iv ketamine, IV lidocaine, epidural analgesia and intrathecal opioids (11). In open-heart surgery, studies have shown that the combination of erector spinae plane (ESP) and superficial parasternal intercostal plane blocks reduces patients' pain scores and the need for postoperative morphine (12).

Cesarean section includes preoperative intrathecal long-acting opioid or epidural long-acting opioids and oral paracetamol. After delivery, intraoperative IV paracetamol, NSAIDs, IV dexamethasone, local wound site infiltrations and regional anesthesia techniques [transversus abdominis plane (TAP) block, ESP block, quadratus lumborum block (QLB)] are recommended if intrathecal morphine was not used. Postoperative oral or intravenous paracetamol, NSAIDs and opioids are recommended as a last-line rescue analgesic if other analgesics have not been used. TENS, Joel-Cohen incision as a surgical technique, non-closure of the peritoneum, and abdominal corsets are also among the current recommendations. Gabapentinoids, IV ketamine, dexmedetomidine and patient-controlled epidural analgesia are not recommended (13).

In patients undergoing elective cesarean section under spinal anesthesia without intrathecal morphine, compared with TAP block, ESP block provides more effective pain relief, has a longer duration of analgesic effect, prolongs the time to first analgesic requirement, is associated with less tramadol consumption. In another study with QLB and ESP block (ESPB), both QLB and ESPB were shown to provide superior analgesia and quality of recovery compared to standard care (14,15).

Video-assisted thoracoscopic surgery (VATS); intraoperative parol and NSAIDs are recommended, although the strength of recommendation is not as high as in other operations. Postoperative paracetamol, NSAIDs, COX inhibitors, and rescue opioids are also recommended at lower levels. Among the regional analgesia techniques, paravertebral block (PVB), ESPB and serratus anterior plane block (SAPB) are recommended as single injection or continuous infusion with catheter technique (16).

SAPB and PVB are well known to reduce pain levels after VATS. The combination of SABP + PVB has been shown to be beneficial for better pain management in VATS compared to SABP or PVB alone (17).

Complex vertebral surgery includes preoperative and intraoperative NSAIDs, COX inhibitors and iv ketamine infusion. NSAIDs and COX inhibitors continue to be recommended in the postoperative period. Although paracetamol is recommended at all stages, the strength of recommendation is not as high as in other surgical procedures. Practices that are not recommended due to limited evidence specific to this procedure include erector spina plane block, iv lidocaine, dexmedetomidine infusion, epidural and intrathecal opioid applications. Although gabapentinoids are not recommended in prospectus data due to their side effect profile, recent publications support the use of perioperative gabapentinoids in vertebral surgery (18).

In a study investigating the effects of analgesic agents administered in vertebral surgeries using intra-operative neuromonitoring, it was observed that high doses of ketamine, dexmedetomidine and lidocaine given as infusion decreased intraoperative neurophysiological monitoring signal quality, while the effects of magnesium, gabapentinoids and methadone could not be measured due to the lack of clinical data (19).

Oncologic breast surgery includes preoperative and intraoperative use of non-steroidal anti-inflammatory agents and gabapentinoids, especially paracetamol and dexamethasone. In addition, regional techniques are recommended and paravertebral plane block is the first choice. In cases without axillary lymph node excision, the use of pectoralis plane block is recommended. Postoperative recommendations include paracetamol, non-steroidal anti-inflammatory agents, COX inhibitors, but rescue opioid analgesia and continuous analgesia through the catheter is recommended if a PVB catheter is available (20). Reduced pain scores and decreased incidence of chronic pain were also observed in patients undergoing oncologic breast surgery who underwent a combination of serratus and pectointercostal plane block (21,22).

Conclusion

In conclusion, in the light of all these data, it is emphasized that post-operative pain management of each procedure must be patient centered. First of all, it is of great importance to recognize pain well and to provide effective treatment in line with multimodal analgesia methods and procedure-specific applications. It should be realized that dynamic postoperative pain control and management can provide early recovery, early ambulation, early rehabilitation and early discharge, as well as preventing the negative effects of inappropriate pain control such as increased complications, chronic pain and prolonged hospital stay.

Ethics

Authorship Contributions

Concept: F.C.Y., F.K., K.Ç., N.A., Design: F.C.Y., F.K., K.Ç., N.A., Analysis or Interpretation: N.A., Literature Search: F.C.Y., F.K., K.Ç., Writing: F.C.Y., F.K., K.Ç., N.A.

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