Perioperative Pain Management

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Key Points

1. Transduction, transmission, and perception are necessary steps in pain physiology. Peripheral and central sensitization are key elements of acute and persistent pain formation.
2. The concept of multimodal analgesia involves the blockade of peripheral and central nociceptors involved in transduction, transmission, and perception of pain.
3. A comprehensive preoperative evaluation and ongoing postoperative assessment of patients, comorbidities, and pain intensity is crucial to provide adequate postoperative pain management.
4. Regional analgesia can be used for a wide variety of surgical procedures. A careful selection of the technique, local anesthetic concentration, and adjuvant analgesic is important to maximize the efficacy of each technique while minimizing adverse events.
5. Continuous intravenous infusion of opioids is not recommended in patients not previously exposed to these medications or those with advance age, sleep apnea, and obesity because their increased risk of respiratory depression.
6. The transmucosal and transdermal are not techniques of choice to treat postoperative acute pain. Iontophoretis delivery of opioids have recently been described and shown some efficacy in postoperative pain management. Acupuncture, transcutaneous electrical nerve stimulation (TENS), and cryoanalgesia are considered non-pharmacological techniques that can be implemented in multimodal analgesic strategies.

30.1 Introduction

It is estimated that 75% of patients undergoing any surgery in the United States experience inadequate pain control [1]. Surgical pain has the features of nociceptive, inflammatory, and neuropathic pain [2]. Therefore, it has been recommended that more than one analgesic modality (multimodal analgesia) will be necessary to achieve adequate perioperative pain control, thus avoiding the unwanted effects of large doses of single analgesics, in particular opioids [3]. A multimodal analgesic technique entails the preoperative initiation, intraoperative continuation, and postoperative maintenance of a combination of regional anesthesia/analgesia techniques (whenever possible) with two or more systemic analgesics. In the postoperative period, the addition of systemic analgesics is important; in particular when regional anesthesia techniques are discontinued, as during this time patients may experience severe distress and discomfort ("analgesic gap period").

30.2 Pain Mechanisms and Pathways

30.2.1 Nociceptors and Nociceptive Afferent Neurons, Wind-Up Phenomenon

Transduction is the first necessary step to convert a noxious stimulus (mechanical, chemical, and thermal) into electrical neural activity. The sensors responsible for detecting noxious stimuli are called nociceptors. Although nociceptors are located in the terminals of sensory afferent fibers with different diameters and velocities of conduction (Aδ[delta] and C fibers); they can also be found in non-neuronal cells such as keratinocytes. After surgical trauma, not one single substance but a myriad of inflammatory mediators (glutamate, ATP prostaglandins, cytokines, bradykinins, neurokinins and growth factors) act on nociceptors to initiate the transduction process. Nociceptors are either ionotropic (ion channel) or metabotropic (second messenger-signaling cascade). The formers rapidly transmit sensory information while the latter are slower responders. Particularly important families of inotropic receptors are the transient receptor potential vanilloid (TRPV) receptors and purinergic receptors [4]. Metabotropic receptors involved in transduction are tumor necrosis factor (TNF) receptor, prostaglandin receptors (EP1-4), leukotriene receptors (BLT1, BLT2, CysLT1 and CysLT2), neurokinin receptors (NK1 and NK2), and growth factor receptors (BDNF and NGF) [4]. The action of the inflammatory mediators on peripheral nociceptors is responsible for the so-called peripheral sensitization. Once the transduction process and peripheral sensitization have been initiated neurons remain in a hyperexcitable state even after cessation of noxious stimulation.

Once a nociceptor is activated the second step necessary is the **transmission** of pain impulses from the peripheral, in the form of electrical signals, to the dorsal horn of the spinal cord. Sodium voltage-gated channels located in Aδ(delta) fibers (small myelinated) and C fibers (unmyelinated) are key in the transmission of electrical impulses. These ion channels are of particular importance because they are the sites of action of local anesthetics. Other ion channels involved in the transmission process include voltage-gated calcium (the site of action of gabapentinoids) and potassium channels.

30.2.2 Dorsal Horn Transmission and Modulation

Once peripheral sensitization (also known as **primary hyperalgesia**) takes place, the spinal cord function receives a barrage of impulses and serves as a relay station. Sensory afferents, interneurons, and ascending and descending projection neurons located in the dorsal horn work coordinately to modulate the sensory information by muting, attenuating, limiting, amplifying, and transmitting pain signals back to the periphery or to supraspinal centers. Wide dynamic range neu-

rons are of particular importance because they participate in the process of central sensitization (**secondary hyperalgesia**) and wind-up, which refers to the frequency-dependent facilitation of the excitability of spinal neurons induced by repetitive electrical stimulation of afferent C fibers [5]. Glutamate is one of the main neurotransmitters in the dorsal horn. There are two major types of glutamate receptors: ionotropic (AMPA and NDMA) and metabotropic. Although both types of receptors contribute for pain transmission, the NMDA receptor has particular clinical relevance because it is the site of action for drugs such as ketamine, methadone, and magnesium sulfate. Thrombospondin-4 (TSP4) is another excitatory neurotransmitter that is increased after nerve injury. TSP4 interacts with voltage-gated calcium channel α(alpha)2δ(delta)1 subunit that is the action site of gabapentin.

30.2.3 Spinal and Supraspinal Neurotransmission and Modulation; Opioid Receptors

From the dorsal horn to cortical structures, sensory pain information is transmitted by the spinothalamic tract and spinobulbar projections. From the thalamus, information regarding location, quality, and intensity of pain reach cortical structures **(perception),** which are activated in a coordinated matter to differentiate between discriminative (somatosensory cortex) and emotional (anterior cingulate and insular cortex) aspects of pain. Activation of the brainstem areas of pain is responsible for the autonomic responses and descending modulation of pain (Fig. 30.1). The periaqueductal grey and the rostral ventral media areas of the brainstem are of utmost important because they modulate afferent signaling by descending facilitation or inhibition and it is the place of action of drugs such as opioids (descending inhibition).

30.2.4 Autonomic Contributions to Pain; Visceral Pain Perception and Transmis sion

A significant interaction exists between the autonomic nervous system and pain responses. An increase in the sympathetic system proportional to noxious stimulation and a decrease of parasympathetic activity occurs in response to acute pain. The magnitude of autonomic response not only correlates with the degree of activity of cortical areas such as the medial prefrontal frontal cortex but also with surgical pain responses. Clinical investigations have found that there is a negative correlation between preoperative baroreflex sensitivity and early and postoperative persistent pain. In fact, it has been suggested that activation of baroreceptors would induce antinociception. Moreover, recent evidence indicates that the contribution of the sympathetic system on acute postoperative pain is significant. The use of a preoperative stellate ganglion blockade resulted in a significant reduction in pain scores and analgesic requirements after upper extremity surgery.

Inflammation, ischemia, and distention (tension receptors) of the gut activate afferent sensory fibers located in the mucosa, muscle, and serosa [6]. The same chemical mediators that activate somatic nociceptors including TRP recep-

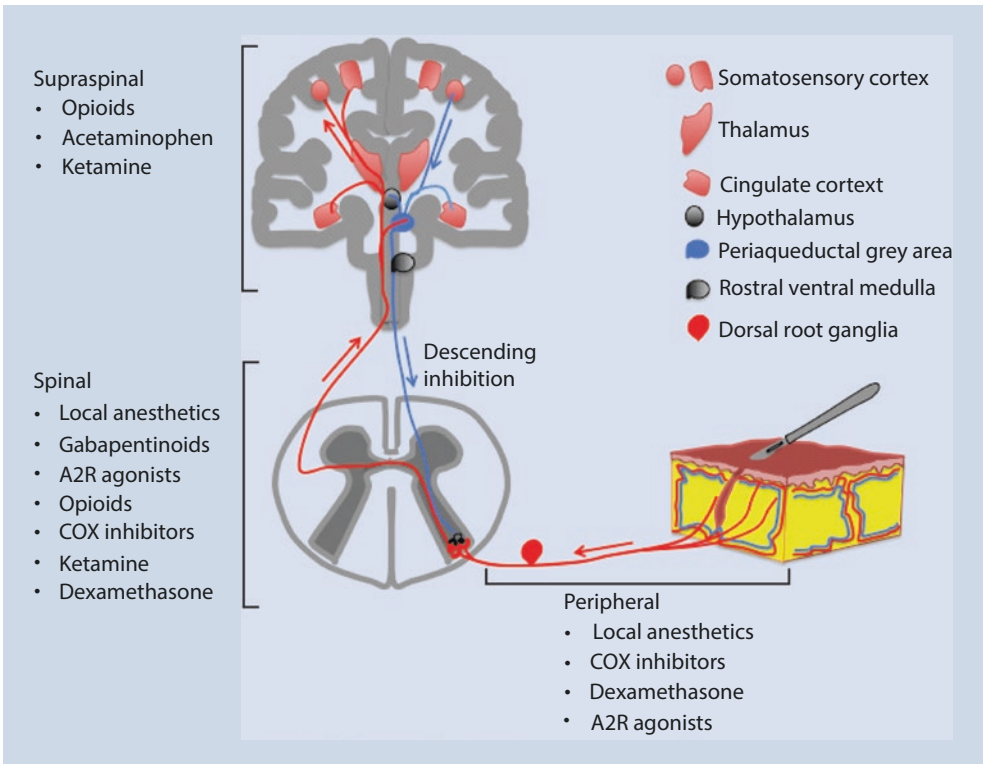

Fig. 30.1 Different places of action of analgesics used in the perioperative period

tors stimulate visceral nociceptors. For instance, ATP, bradykinins, and prostaglandins are able to induce depolarization of visceral sensory afferents. Vagal afferents have their cell bodies in the nodose and jugular ganglia, and innervate all thoracic and abdominal viscera including part of the colon; on the other hand, spinal afferents have their cell bodies in the dorsal root ganglia and uniformly innervate all the viscera. Both vagal and spinal nerves afferents are responsible for conveying information from the gastrointestinal tract to the central nervous system. It has been postulated that vagal fibers transmit physiological information while spinal nerves are responsible for conveying noxious stimulation. Once the afferent neurons reach the spinal cord, they make synaptic connections with second-order neurons that will project to the thalamus and nucleus tractus solitarious via the spinothalamic, spinoreticular, and dorsal column pathways. Significant interactions between somatic and visceral afferents are responsible for the so-called referred pain [6]. Descending inhibition also plays a role in visceral pain. It has been demonstrated that low doses of opioids can activate descending pathways and cause antinociception.

30.2.5 Social, Vocational, and Psychological Influences on Pain Perception

Preoperative social experiences, psychological factors (i.e., anxiety and depression) and patients' expectations have significant impact on postoperative pain perception and development of postoperative persistent pain. For instance, alexithymia, the inability to identify and express emotions, predicts the development of postoperative persistent pain after mastectomy. Along this evidence, a preoperative diagnosis of severe/definite depression or preoperative self-perceived risk of addiction is also associated with a significant increase in the risk of postoperative persistent pain. Coping strategies also can be useful to predict postoperative pain outcomes. Thus, catastrophizing patients may misinterpret and exaggerate situations since they are perceived as threatening and report worse quality of life and activity levels after surgery.

Lastly, inadequate postoperative pain management can also be associated with the development of psychiatric disorders after surgery. For instance, patients with high postoperative pain scores appear to be at risk for depression and post-traumatic stress disorder 1 year after surgery. On the other hand, perioperative cognitive interventions targeted to improve depression postoperatively have shown to decrease pain scores and improve quality of life after cardiac surgery.

30.2.6 Sex and Age Differences in Pain Perception

Overall, women are more likely to report a variety of recurrent pain, more severe and frequent compared to men. In the context of surgery, women reported higher pain scores than men after a variety of surgeries [7]. Furthermore, women show slower recovery and have a higher risk of developing postoperative persistent pain than men. This can be explained by (1) biological factors: signs of central sensitization are less pronounced in men than women, while descending inhibition control is less efficient in women than men; (2) psychological factors: differences in coping strategies; (3) social factors (expectations); and (4) past medical history [8].

30.2.7 Persistent Postoperative Pain

Persistent postoperative pain (PPP) is defined as pain that persists after surgery longer than 3 months' duration, after exclusion of other causes. Direct nerve injury (transection, stretching, or crushing) has been indicated as the cause ("primary injury"). This primary injury to the nerve is the initial step in a series of events that involves the interaction of injured and non-injured axons, resident non-neuronal cells, and immune cells. The incidence of PPP ranges from 5% to 50%. PPP can occur after major and minor surgery, and open and laparoscopic procedures; however, its incidence appears to be lower after video-assisted surgery. Risk factors include female gender, preoperative pain, diabetes mellitus, poorly managed acute postoperative pain, operative time, tissue ischemia, anxiety, and depression (Table 30.1) [2].

PPP is common after thoracic surgery (post-thoracotomy pain syndrome), breast surgery (postmastectomy pain syndrome), limb amputations (phantom limb syndrome), and total knee replacements [9]. PPP has features of neuropathic pain, thus patients usually report pain as burning, tingling, numbing, or electric-like shocks 1 or 2 dermatomes around the surgical incision.

To date there are no pharmacological agents that have demonstrated efficacy in the prevention of PPP. While gabapentinoids and ketamine have shown modest effect; regional anesthesia has shown promising results in the prevention of PPP [10].

Table 30.1 Predictor factors and causes of persistent postoperative pain

Causes	Predictors
Nerve injury	Female gender
Prolonged tissue ischemia	Preoperative pain
	Anxiety – Depression – Catastrophizing
	Diabetes mellitus (TKA)
	Operative time
	Open > minimally invasive procedures
	Type of surgery (thoracotomy, mastectomy, TKA and limb amputations)
	Exaggerated acute postoperative pain

TKA total knee replacement

30.3 Pain Management

30.3.1 Pharmacologic

Drugs

Opioids provide adequate postoperative analgesia, but their routine use is often limited by adverse effects. The mechanism of action of opioids is by binding mainly to mu receptors, which results in hyperpolarization of sensory neurons, thus decreasing the release of neurotransmitters involved in nociception. In the perioperative period, opioids are typically administered intravenously, neuraxially, orally, and less often sublingually and transdermally. Intravenous patient controlled analgesia (IVPCA) is a commonly used technique in the postoperative period of any major surgery (Table 30.2). Fentanyl, morphine, and hydromorphone are the most commonly used opioids for IVPCA. Intrathecal opioids provide adequate analgesia during and after surgery. Fentanyl, sufentanil, morphine, and hydromorphone are often used for neuraxial analgesia (Table 30.3). Oral opioids are also available and are often used in the ambulatory setting or when systemic opioids are not required after major surgery. Oxycodone, hydrocodone, tramadol, and codeine are frequently used when patients are able to tolerate at least liquids per mouth. Opioids are associated with side effects including respiratory depression, nausea and vomiting, ileus, drowsiness, urinary retention, confusion, and hyperalgesia [11]. Therefore, the judicious use of these drugs is recommended in the perioperative period. Tramadol is a weak μ(mu)-opioid agonist and norepinephrine and serotonin reuptake inhibitor with questionable efficacy as a single agent that has proven to be effective when given in combination with other analgesics.

Non-steroidal anti-inflammatory drugs (NSAIDs) are adjuvant analgesics with proven efficacy in the context of multimodal analgesia for surgery (Table 30.4). Their mechanism of action is inhibition of COX-1/COX-2. The concept of COX selectivity denotes the extent to which these drugs are able to inhibit one enzyme isoform relative to the other at half maximal inhibitory concentrations. Interestingly, the same drug might show COX-1/COX-2 ratios at distinct inhibitory concentration levels, therefore each COX inhibitor has its own selectivity (Table 30.2). In other words, one analgesic can be more or less selective depending on the dose used. NSAIDs have several routes of administration depending on the type of drug. Ketorolac is one of the most commonly used NSAIDs in the perioperative period because of its strong analgesic properties and the fact that it can be administered orally, sublingually, and intravenously. Other intravenous NSAIDs, although not all available in the United States, include diclofenac, ibuprofen, dexketoprofen, flurbiprofen axetil, and lornoxicam. Overall, NSAIDs can be administered safely in the perioperative period; however, their use, in particular ketorolac, should be limited to short

Table 30.2 Common solutions for intravenous patient (adult) controlled analgesia

Solution	Bolus	Interval	Basal rate	Max. dose hour
Morphine	0.5–2 mg	5–10 min	1 mg/h	6 mg
Fentanyl	5–20 μ(mu)g	5–10 min	10 μ(mu)g/h	60 μ(mu)g
Hydromorphone	0.1–0.2 μ(mu)g	5–10 min	0.2 mg/h	1.2 mg

Solutions and type of opioid used for IVPCA should be administered considering patients' expectations, comorbidities and type of surgery

Table 30.3 Recommended solutions for epidural and peripheral nerve catheter patient controlled analgesia

Route	Local anesthetic	Additives	Basal rate	Bolus	Interval
Epidural	Ropicavaine 0.05–0.2% Bupivacaine 0.0625–0.125%	Fentanyl 5–10 μ(mu)g/mL Sufentanil 0.25–2 μ(mu)g/mL Hydromorphone 3–10μgml Clonidine 1.5 μ(mu)g/mL	3–8 mL/h	3–5 mL	10–15 min/4–6 doses/h
Peripheral nerve catheter	Lidocaine 1% Bupivacaine 0.125–0.25% Ropivacaine 0.1–0.2%	Fentanyl 1–2 μ(mu)g/mL Sufentanil 0.1 μ(mu)g/mL Hydromorphone 3–10μg/ml Clonidine 1–2 μ(mu)g/mL	3–10 ml/h	10–12 mL	60 min/1 dose/h

Solutions and doses of local anesthetics and additives should be administered considering patients' expectations, comorbidities, and location and type of surgery

Table 30.4 Recommended doses of commonly used non-opioid analgesics

Route	Name	Dose	Adverse effects/comments
Intravenous	Acetaminophen	1 gram every 6–8 h	Liver failure
	Ketorolac	15–30 mg every 6–8 h	Renal impairment, bleeding and gastric erosion/PUD[a]
	Diclofenac sodium	18.75–50 mg every 6–8 h	Renal impairment, bleeding[a]
	Ibuprofen	800 mg every 6 h	Renal impairment, bleeding[a]
Oral	Naproxen	250–500 mg every 6–12 h	Renal impairment, bleeding[a]/Delayed onset of effect
	Ibuprofen	200–400 mg every 6 h	Renal impairment, bleeding[a]
	Ketorolac	15–30 mg every 8 h	Renal impairment, bleeding[a]
	Celecoxib	200 mg every 12 h	Anastomotic leak
	Pregabalin	75–150 mg every 12 h	Sedation, confusion, dizziness
	Gabapentin	100–300 mg every 8 h	Sedation, confusion, dizziness

Doses of NSAIDs and other analgesics should be administered considering patients' expectations, comorbidities, and type of surgery
PUD peptic ulcer disease
[a]The short-term use of NSAIDs has demonstrated no serious gastrointestinal outcomes such as bleeding or perforation or cardiovascular events

periods of time; and avoided in patients with coagulopathy, renal failure, or history of peptic ulcer [3].

Among the selective COX-2 inhibitors (parecoxib, etoricoxib and lumiracoxib), celecoxib (oral) has been the most commonly used in the perioperative period after rofecoxib and valdecoxib were withdrawn from the United States market. Although, their main advantage over non-selective COX inhibitors is a lower incidence of gastrointestinal complications, recent concerns regarding an increase in major adverse cardiovascular events and anastomotic leakage after colorectal surgery has been raised with the use of non-selective and selective COX-2 inhibitors [3, 12, 13].

Acetaminophen (intravenous, rectal, or oral) is widely used in the context of multimodal analgesia. The mechanism of analgesia of acetaminophen is still unclear; however, it can be related to a dose-dependent reduction of PgE and activation of $5HT_3$ receptors in the central nervous system. Intravenous acetaminophen has the advantage over the oral or rectal formulations in that it is associated with about a 2-fold the plasma and effect site concentration; which can explain the superior analgesic efficacy and improved patient satisfaction [14]. Acetaminophen reduces morphine consumption by 20% and postoperative nausea and vomiting. This last effect can be attributed to (1) its analgesic effect, and (2) increase in anandamide levels [15]. Acetaminophen has a duration of action of 4–6 h and can be administered every 6–8 h. A maximum dose of 3 g is recommended to avoid hepatoxicity. Its lack of interference with platelet function and safe administration in patients with a history of gastrointestinal bleeding, peptic ulcers, or asthma makes acetaminophen preferable over NSAIDs [3].

Gabapentinoids (pregabalin and gabapentin) are adjuvant drugs with analgesic and opioid-sparing effects. Their mechanism of action is through binding of α(alpha)2δ(delta) and thrombospondin receptors in the central nervous system. Pregabalin (75–150 mg) is commonly given orally before surgery and postoperatively every 12 h. In comparison to gabapentin, pregabalin is associated with less sedation and cognitive disturbances. Gabapentin can be administered orally three times a day (100–1200 mg); however, the side effects associated with large doses are disadvantageous when its use is considered in the perioperative period, mainly in elder patients [3].

Dexamethasone (intravenous) is a potent glucocorticoid that has anti-inflammatory and analgesic effects. The exact mechanism of analgesia of dexamethasone is still not clear but it appears to be related to the anti-inflammatory effects (down-regulation of cyclooxygenase-2 mRNA). Epidural dexamethasone may be acting at spinal sites by inducing the synthesis of the phospholipase-A2 inhibitory protein lipocortin, and modulating the activity of the glucocorticoid receptor at the level of the substantia gelatinosa. Dosages (4–10 mg) commonly used for postoperative nausea and vomiting prophylaxis are effective to provide analgesia and have demonstrated not to interfere with wound healing or increase the rate of complication after major surgery [3]. Dexamethasone does not prevent the formation of persistent postoperative pain [16]. Dexamethasone has also shown to prolong and enhance the quality of peripheral nerve blockades; although, it is unknown whether this effect is related to the systemic absorption of the drug or locally at the nerve level.

Ketamine (intravenous or epidural) is an NMDA receptor antagonist that has strong analgesic and opioid-sparing properties [17]. Other mechanisms for ketamine-induced analgesia include direct action on monoaminergic, cholinergic, and mu receptors. Subanesthetic (or analgesic) doses of 3–5 mg/kg/min given during surgery and/or postoperatively have been shown to provide effective analgesia for a wide range of procedures [17]. Nistagmus, diplopia, blurred vision, and hallucinations are side effects reported even with low doses of ketamine, although their incidence is low (<1%) [17]. The preventive effects of ketamine on postoperative persistent pain formation are observed after its intravenous but not the epidural administration.

Intravenous infusions of **lidocaine** are commonly used in protocols of multimodal analgesia because it reduces intraoperative requirements of opioids and postoperative nausea and vomiting, improves gastrointestinal motility, and shortens length of stay; although these beneficial effects appear to be surgery specific. The mechanism of action of lidocaine is related to its properties as a local anesthetic and anti-inflammatory effect. The infusion (1.5–4 mg/kg/h) of this amide local anesthetic can be used intra- and/or postoperatively, although the maximum benefit appears related to the use of this drug during surgery compared to short-term postoperative infusions. Adverse events associated with the use of lidocaine are very low and mostly related to its actions on the central nervous system (perioral numbness, confusion, and visual disturbances). The use of perioperative intravenous lidocaine can reduce the incidence of postoperative persistent pain [18].

Esmolol (a selective ultra-short beta-blocker) has been used in intravenous infusions (loading dose of 0.5 mg/kg followed by 5 μ[mu]g/kg/min) to provide analgesia in major surgery. The mechanism of analgesia of esmolol is not fully understood, although it appears to be related to the activation of G proteins at a central level, which resembles the effect of clonidine. Intraoperative infusions of esmolol have not only been shown to provide adequate analgesia and hemodynamic stability but also have opioid- and anesthetic-sparing effects. Bradycardia and hypotension can be observed during infusions of larger doses than recommended.

Intravenous or intrathecal **magnesium sulfate** has analgesic effects. Magnesium sulfate appears to exert analgesia by at least 2 mechanisms: (1) regulation of calcium influx into neurons and (2) antagonism of the NMDA receptors at central levels. It can significantly potentiate the antinociception of drugs such as ketamine and reduce the consumption of opioids. It is commonly used intraoperatively and administered as a bolus (30–50 mg/kg) followed by a continuous infusion (8–15 mg/kg/h). Intrathecal administration of 50 mg of magnesium sulfate can delay the onset of sensory block and prolong the duration of motor block produced by local anesthetics. Hemodynamic instability (bradycardia and hypotension) and muscle weakness are commonly reported adverse events associated with the use of intravenous magnesium. Thus, caution should be advised in the dosage of muscle relaxants or in the use of other anesthetics that can trigger hemodynamic stability when magnesium sulfate is used during surgery.

Dexmedetomidine and clonidine are α(alpha)2-adrenoreceptor agonists with known analgesic effects. The mechanism of action is activation of the α(alpha)2-adrenoreceptor that results in depression of the release of presynaptic C-fiber transmitters and hyperpolarization of postsynaptic dorsal horn neurons. Both agents have anesthetic- and opioid-sparing properties and can be used systemically (intravenous) or along with local anesthetic solutions for regional analgesia. As adjuvants for peripheral nerve blocks or neuraxial analgesia (intrathecal or epidural) both drugs can (1) accelerate onset and prolong the duration of the motor and sensory blockade, (2) decrease the concentration of local anesthetics needed for surgical blockade, (3) prolong the time to the first rescue analgesic requirement, and (4) improve patient satisfaction; however it is worth considering that these clinical effects are not consistent. Although, compared with clonidine, dexmedetomidine may avoid the undesirable cardiovascular effects related to α(alpha)1 adrenoreceptor activation bradycardia, hypotension, and sedation are adverse events associated with the use of both drugs.

Neostigmine is an acetylcholinesterase inhibitor that can be administered in the epidural (1–10 μ[mu]g/kg) space or intrathecally (1–100 μ[mu]g) [19]. Neostigmine causes dose-dependent analgesia, potentiates opioid-induced analgesia, and reduces the requirements of other analgesics. It does not influence the dynamics of the blockade provided by local anesthetics [20]. The mechanism of action appears to be related to an increase in the concentration of the neurotransmitter acetylcholine that, in turn, acts on muscarinic M1 and M3 and presynaptic nicotinic receptors located in interneurons at the laminae II and V of the dorsal horn. Side effects are dose-dependent and include nausea and vomiting, headache, and hemodynamic disturbances [20].

Despite being used as an anxiolytic, intrathecal **midazolam** (1–2 mg) has shown analgesic properties [21]. The mechanism of action is still unclear but it can be related to the activation of $GABA_{A,}$ benzodiazepine receptors, and release of endogenous opioids. It causes dose-dependent acceleration of the onset of motor/sensory block, prolongation of the duration of analgesia and a reduction in the consumption of opioids [21]. Sedation has been reported as an adverse event associated with the use of intrathecal midazolam [21].

Antidepressants are commonly used for the treatment of chronic pain syndromes and several trials have been conducted to evaluate their efficacy in the context of surgical pain. Antidepressants can be grouped in three different classes: (1) tricyclic antidepressants, (2) selective serotonin reuptake inhibitors, and (3) serotonin and norepinephrine reuptake inhibitors. Their mechanism of analgesia can be explained by central and peripheral actions and include an increase in the synaptic concentrations of serotonin and norepinephrine, modulation of peripheral sodium channels, and NMDA receptors. The literature does not support the use of antidepressant for treatment of acute, or prevention of chronic, postoperative pain [22]. Adverse events include somnolence, dizziness, nausea, diarrhea, constipation, shivering, somnolence, and tingling of extremities and appear to be drug specific [22].

30.3.2 Routes

Intravenous, Subcutaneous, and Intramuscular Analgesia

Intravenous analgesia is the preferred analgesia modality in patients with a non-functional gastrointestinal tract, those in whom regional analgesia is not indicated, or to treat breakthrough pain. Based on this, intravenous patient-controlled

analgesia (IVPCA) is still one of the most commonly used analgesic techniques to manage postoperative acute pain. It consists of the intravenous administration of analgesics, most commonly opioids, self-controlled by the patient. A particular concern is that IVPCA cannot be indicated in all patients (i.e., infants or patients with dementia). Although, IVPCA provides superior analgesia than "around the clock" techniques it is still not better than regional analgesia or multimodal techniques. Furthermore, opioid consumption is still higher in patients treated with IVPCA than regional analgesia; therefore patients are still at risk for opioid-related side effects [23]. The intramuscular and subcutaneous routes are less preferred in the context of surgery because they are associated with pain and erratic absorption of analgesics.

Regional Anesthesia Techniques

When possible, regional analgesia should be considered as one of the techniques of choice to provide adequate postoperative analgesia. It is not only superior in terms of postoperative pain to intravenous analgesic control and patient satisfaction, but also might improve other clinical outcomes such as cardiovascular and pulmonary complications in appropriately selected patients [24]. The concept of patient controlled analgesia (PCA) is also applicable for regional anesthetic techniques where a catheter is in place (Table 30.3). Patient-controlled epidural analgesia is one of the most commonly used forms of PCA to manage postoperative pain after abdominal or thoracic surgery.

The choice of any regional analgesic technique should be based on several factors, including patient age and comorbidities, anatomic location of the surgical incision, and patient expectations. For instance, patients receiving antiplatelet medications or anticoagulation should be treated according to the American Society of Regional Anesthesia guidelines to diminish the risk of spinal hematomas. The administration of opioids in the epidural space or intrathecally should be considered with caution in patients at risk of respiratory depression in particular with the use of hydromorphone or morphine.

Neuraxial techniques (spinal, epidural, or combined spinal epidural), peripheral nerve blocks with and without continuous infusions of local anesthetic solutions, wound infiltrations with and without infusion of analgesics, field blocks, and intra- or periarticular anesthetic infiltrations have been successfully used as regional anesthesia/analgesia techniques in multimodal analgesic approaches for a wide variety of surgical procedures [25].

Neuraxial analgesia can be used for thoracic, abdominal, or lower extremity surgery. Hypotension, motor weakness, urinary retention, and opioid-induced respiratory depression can be associated with the use of neuraxial analgesia, in particular with high concentrations of local anesthetics and opioids [26]. Peripheral plexus or selective nerve blockade have become a cornerstone piece in any multimodal analgesia regimen for orthopedic surgical procedures. Catheter-based techniques consist of the continuous infusion of local anesthetics with the goal of prolonging analgesia. Catheters are placed in the proximity of plexus or single nerves and can be maintained for several days after surgery, even in the ambulatory setting. Motor weakness and catheter dislodgment are common concerns associated with the use of catheters. More recently, the introduction of the transverse abdominis plain (TAP) block, paravertebral blocks, rectus sheath block, and thoracic wall blocks (PECs blocks) with or without catheters have been shown to be a valuable option in patients in whom more "traditional" regional anesthetic techniques are contraindicated or difficult to perform due to anatomic abnormalities [27].

When epidural analgesia and paravertebral block are contraindicated, intrapleural (IB), extrapleural (EB), and intercostal nerve blocks (INB) can be considered for postoperative pain relief after thoracic or upper abdominal surgery [28, 29]. Although IB and INB are superior to intravenous analgesia, they do not provide similar quality of analgesia to epidural or paravertebral blocks. EB consists of creating a space between the parietal pleura and thoracic wall and placing a catheter that will be used to administer a solution of local anesthetic after completion of the thoracotomy. INB can be done by direct visualization during thoracotomy or percutaneously. Two to five milliliters of local anesthetic is injected inferior to the rib to avoid intravascular injection over 2–3 spaces above and below the incision. Single or intermittent boluses or continuous administration of local anesthetics through catheters can be used for IB and INB. Although the rate of complications of IB and INB are low, both blocks have a risk of local anesthetic toxicity and pneumothorax [28, 29]. Recently, the use of liposomal bupivacaine for posterior intercostal nerve blocks has been described for patients who underwent thoracic surgery. Interestingly, this technique provided similar postoperative pain control to epidural analgesia.

A liposomal formulation of the local anesthetic bupivacaine is clinically available. The duration of analgesia with liposomal bupivacaine is approximately 48 h. Although, the current recommended use of liposomal bupivacaine is for surgical wound infiltration only, a recent human volunteer study has shown that it can be safely used for peripheral nerve blocks, and provide a duration of sensory and motor block of over 24 h. Unfortunately, the quality of the blockade appears to be highly variable. With the purpose of extending the duration and improving the quality of analgesia, different solutions of local anesthetics (i.e., ropivacaine and bupivacaine) with drugs such as ketorolac, buprenorphine, dexamethasone, clonidine, or dexmedetomidine, and/or epinephrine can be used for peripheral nerve blocks, intra-articular injections, or wound infiltrations [30].

A single-dose extended-release formulation of morphine is also commercially available. The epidural administration of this liposomal-based formulation results in a sustained release of morphine. Extended release epidural morphine (EREM™) has been used in context of multimodal analgesia with good clinical results.

Transmucosal and Transdermal Routes

The transmucosal (TM) and transdermal (TD) routes of administration have been described to provide analgesia after surgery. Fentanyl can be delivered through both routes but the transmucosal is not preferred and not recommended in the postoperative period. On the other hand, an iontophoretic transdermal system (ITS) has been recently released in the market and shows to be as efficacious and cause less opioid-related adverse event than morphine IVPCA [31]. This new technology employs the use of a micro electric current (170 μ[mu]A) to deliver 40 μ(mu)g of fentanyl upon a patient's request (patient controlled analgesia). Although, the first initial serum concentrations of fentanyl are lower using ITS than the intravenous route, the following systemic concentrations will increase over time until they are comparable to those achieved by intravenous administration.

30.4 Other Techniques

There is a growing interest in investigating alternative therapeutic approaches to provide analgesia and reduce opioid consumption in patients with acute surgical pain. Cryotherapy, acupuncture, transcutaneous electrical nerve stimulation (TENS), and hypnosis are the most commonly used techniques. Cryotherapy (cryoanalgesia) applies a cryoprobe whereby carbon dioxide or nitrous oxide is released at a high pressure and causes cooling of the probe tip to temperatures of −50 to −80 °C. This technique has been used to manage patients with acute and chronic pain with some efficacy in providing analgesia for acute postoperative pain; however, it has been associated with postoperative persistent pain formation after its application on neural structures [32].

Acupuncture is an Asian medical treatment that has been used in the perioperative period to treat postoperative nausea and vomiting and to provide analgesia. The mechanism of acupuncture-induced analgesia is still unknown but several theories have been speculated including the release of enkephalin, β(beta)-endorphin, endomorphin, endocanabinoids, and modulation of the autonomic system. Several acupoints such as ST34 (knee), ST36 (knee), KI6 (ankle), LI4 (hand), and P6 (forearm), and modes of stimulation including manual traditional and electric have been used to provide analgesia. Among those modalities, electrical stimulation appears to be more effective than manual. Although, the results of clinical trials are conflicting, the evidence suggests that the opioid- and anesthetic-sparing effects of acupuncture are clinically relevant when this technique is used before induction of anesthesia since the onset takes 15–30 min.

TENS (transcutaneous nerve electrical stimulation) is a non-invasive technique used to provide postoperative analgesia. Its mechanism of action is based on the gate theory of pain. Thus, it is postulated to be electrical stimulation through the skin inhibiting the transmission of pain impulses through the spinal cord, as well as the release of endogenous opioids, as endorphins, by the brain or the spinal cord. It has been shown to provide analgesia and reduce analgesic consumption after cardiac surgery, cholecystectomy, and neck surgery, but not to be effective following thoracotomy and bone marrow aspiration [33].

30.5 Questions and Answers

Questions (Choose the Most Appropriate Answer)

1. Mechanisms necessary for pain formation and discrimination are the following, except:
   A. Transduction
   B. Transmission
   C. Perception
   D. Convection
2. Peripheral sensitization is responsible for:
   A. Primary hyperalgesia
   B. Secondary hyperalgesia
   C. Tertiary hyperalgesia
   D. Hyperacusis
3. Central sensitization is responsible for:
   A. Primary hyperalgesia
   B. Secondary hyperalgesia
   C. Referred hyperalgesia
   D. Hyperosmia
4. Adequate planning on the postoperative pain management should include the following factors:
   A. Type and location of surgery
   B. Patient's commorbitdies
   C. Patient's social and psychological perception of pain
   D. All of the above
5. Multimodal analgesic therapy involves:
   A. The administration of intravenous analgesic only
   B. The use of regional analgesia only
   C. The use of hypnosis and acupuncture only
   D. The pharmacological and non-pharmacological therapies
6. Regional anesthesia is indicated for:
   A. Abdominal surgery only
   B. Thoracic surgery only
   C. Orthopedic procedures only
   D. It is indicated in a wide variety of surgical procedures
7. Intravenous opioids analgesics are:
   A. The only analgesic that can be used for postoperative pain management
   B. The most effective analgesic for postoperative pain
   C. Associated with few adverse events
   D. Recommended as part of a multimodal analgesic regimen
8. The use of COX inhibitors are recommended:
   A. As part of a multimodal analgesic technique
   B. Only minimally invasive surgical procedures
   C. In patients with recent history of renal failure
   D. In patients with recent history of peptic ulcer disease

9. A healthy 48-year-old woman is scheduled for open pancreatic surgery. An effective multimodal analgesic technique should include:
   A. Only intravenous and neuraxial opioids
   B. Only epidural analgesia
   C. A continuous infusion of intravenous opioids plus preoperative COX-inhibitors
   D. Patient controlled-epidural analgesia (low concentration of local anesthetic and opioid) plus perioperative use of COX-inhibitors and/or acetaminophen plus tramadol. Breakthrough pain can be rescued with intravenous opioids.
10. A 55-year-old male with history of severe sleep apnea is scheduled for a thoracotomy. The following analgesic strategies can be used effectively and safely except:
    A. Patient-controlled epidural analgesia plus 1 g of acetaminophen (every 8 h) plus 75 mg of pregabalin preoperatively
    B. Paravetebral block plus 48 h of 30 mg of intravenous ketorolac (every 8–12 h) plus 1 gm of acetaminophen (every 8 h)
    C. Continuous intravenous opioid analgesia 50 μg of fentanyl/hour
    D. Intercostal block plus 48 h of 30 mg of intravenous ketorolac (every 8–12 h) plus 1 gm of acetaminophen (every 8 h) plus patient controlled intravenous fentanyl analgesia (10 μg every 10–15 min, no basal rate)

Answers

1. **D.** Convection is heat transfer by mass motion of a fluid such as air or water when the heated fluid is caused to move away from the source of heat, carrying energy with it.
2. **A.** Peripheral sensitization occurs when inflammatory mediators stimulate polymodal nociceptors in which they cause a drop in the excitatory thresholds. As a result of peripheral sensitization, noxious stimuli evoke a stronger response in nociceptors.
3. **B.** Central sensitization can occur after inflammation or nerve damage. Neurons in the dorsal horn of the spinal cord undergo significant changes including expansion of the receptive fields, increased responses (wind-up) and lowering of the thresholds.
4. **D.** Postoperative pain management involves multidimentional and multidisciplinary care. Understanding of surgical (minimally invasive versus open), patient's comorbidities (extreme age, obesity or obstructive spleep apnea), and psychological factors (anxiety, depression, alexithymia) are crucial to decide and plan on multimodal pain strategies.
5. **D.** Multimodal analgesia refers as the use of a variety of pharmacological and non-pharmacological therapies with the objective of minimizing trauma and decreasing nociceptive signals from injured tissues, spinal cord and supraspinal sites of the nervous system.
6. **D.** Different techniques including neuraxial procedures, blockade of plexus or peripheral nerves, wound infiltration or infusion of local anesthetic solution in different planes of the surgical wound and administration of analgesics or local anesthetics in virtual anatomic spaces (i.e., transverse abdominis plane or paravertebral space) have been used to provide postoperative analgesia to surgical patients.
7. **D.** Intravenous, neuraxial and oral opioids are commonly used intra- or postoperatively to provide analgesia. However, their use has been associated with side effects including respiratory depression, nausea and vomiting, ileus, drowsiness, urinary retention, confusion, and hyperalgesia. Therefore, the judicious use of these drugs is recommended in the perioperative period.
8. **A.** Non-steroidal anti-inflammatory drugs are adjuvant analgesics with proven efficacy in the context of multimodal analgesia for surgery. Overall, NSAIDs can be administered safely in the perioperative period; however, their use, in particular ketorolac, should be limited to short periods of time; and avoided in patients with coagulopathy, renal failure, or history of peptic ulcer.
9. **D.** A multimodal analgesic regimen is recommended in the management of this patient to avoid the adverse event of each drug and decrease nociceptive signals from injured tissues, spinal cord and supraspinal sites of the nervous system.
10. **C.** Epidural, paravertebral block and intercostal nerve blocks can be considered for postoperative pain relief after thoracic surgery in combination with COX-inhibitors, acetaminophen and opioid intravenous patient control analgesia. Continuous infusion of opioids in patients with history of sleep apnea is not recommended because of an increased risk of respiratory depression.

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