Chapter

40 PERIOPERATIVE PAIN MANAGEMENT

Meredith C.B. Adams and Robert W. Hurley

Postoperative pain is a complex physiologic reaction to tissue injury. Commonly, patients' primary concern about surgery is how much pain they will experience following the procedure. Postoperative pain produces acute adverse physiologic effects with manifestations on multiple organ systems that can lead to significant morbidity (Box 40.1). For example, pain after upper abdominal or thoracic surgery often leads to hypoventilation from splinting. This promotes atelectasis, which impairs ventilation-to-perfusion relationships, and increases the likelihood of arterial hypoxemia and pneumonia. Pain that limits postoperative ambulation, combined with a stress-induced hypercoagulable state, may contribute to an increased incidence of deep vein thrombosis. Catecholamines released in response to pain may result in tachycardia and systemic hypertension, which may induce myocardial ischemia in susceptible patients. In a 2015 observational study, 54% of patients experienced moderate to extreme acute postoperative pain at the time of their discharge from the hospital.[1] This represents an insignificant or slight improvement in postoperative pain management as compared to an earlier (2003) study in which 64% of patients had the same level of pain at hospital discharge.[2] However, it is concerning that in the more recent study[1] 46% of the patients had moderate to extreme level of postoperative pain 2 weeks following discharge.

Factors that positively correlate with severity of postoperative pain include preoperative opioid intake, increased body mass index, anxiety, depression, pain intensity level, characteristics of fibromyalgia, and the duration of surgical operation. Factors that are negatively correlated include the patient's age and the level of the surgeon's operative experience. Although these findings have been replicated in numerous studies, the immediate postoperative pain assessment may suffer from significant observer bias. Besides the postoperative pain-related factors, the accepting postanesthesia care unit (PACU) nurse had a greater impact on the initial postoperative pain score than the anesthesiologist's intraoperative care.[3]

Box 40.1 Adverse Physiologic Effects of Postoperative Pain

Pulmonary System (decreased lung volumes)
Atelectasis
Ventilation-to-perfusion mismatching
Arterial hypoxemia
Hypercapnia
Pneumonia

Cardiovascular System (sympathetic nervous system stimulation)
Systemic hypertension
Tachycardia
Myocardial ischemia
Cardiac dysrhythmias

Endocrine System
Hyperglycemia
Sodium and water retention
Protein catabolism

Immune System
Decreased immune function

Coagulation System
Increased platelet adhesiveness
Decreased fibrinolysis
Hypercoagulation
Deep vein thrombosis

Gastrointestinal System
Ileus

Genitourinary System
Urinary retention

A perioperative plan should be developed that encompasses these factors in order to lessen the severity of the patient's postoperative pain. Despite having a lower predictive risk for postoperative pain, elderly patients can represent significant management challenges (also see Chapter 35). Elderly patients are at a greater risk than younger patients for cognitive dysfunction in the perioperative period because of various factors, including increased sensitivity to drugs and other medical comorbid conditions. Patients taking opioids for chronic pain relief preoperatively have higher pain scores, more opioid consumption, and lower pain thresholds in the immediate postoperative period. Perioperative management plans that incorporate these variables may favor the use of regional anesthesia because of the decreased mortality rate and infrequent incidence of postoperative cognitive dysfunction and pain (also see Chapters 17 and 18). Preemptive regional analgesia may enhance pain control, decrease adverse cognitive effects, and improve postoperative recovery overall. Well-controlled pain postoperatively will enhance postoperative rehabilitation, which may improve short- and long-term recovery as well as the quality of life after surgery.

Postoperative pain also may have long-term consequences as well. Poorly controlled postoperative pain may be an important predictive factor for the development of chronic postsurgical pain (CPSP),[4] defined as pain after a surgery lasting longer than the normal recuperative healing time. CPSP is a largely unrecognized problem that may occur in 10% to 65% of postoperative patients, with 2% to 10% of these patients experiencing severe CPSP.[5] Transition from acute to chronic pain occurs very quickly, and long-term behavioral and neurobiologic changes occur much earlier than previously anticipated.[6] CPSP is relatively common after surgical procedures, such as limb amputation (30% to 83%), thoracotomy (22% to 67%), sternotomy (27%), breast surgery (11% to 57%), and gallbladder surgery (up to 56%).[7]

Improved understanding of the epidemiology and pathophysiology of postoperative pain has increased the use of multimodal management of pain in an effort to improve patient comfort, decrease perioperative morbidity, and reduce cost by shortening the time spent in PACUs, intensive care units, and hospitals. Multimodal approaches involve the use of multiple, mechanistically distinct medications with the application of peripheral nerve or neuraxial analgesia. The added complexity of a true multimodal approach to perioperative pain requires the formation of perioperative pain management services, most often directed by an anesthesiologist or pain medicine physician.

COMMON TERMINOLOGY

- *Pain (nociception):* Pain is described as an unpleasant sensory and emotional experience caused by actual or potential tissue damage, or described in terms of such damage.[8]
- *Acute pain:* Acute pain follows injury to the body, and generally disappears when the bodily injury heals. For instance, acute pain occurs during the time needed for inflammation to subside or for acute injuries, such as lacerations or incisions, to repair with the union of separated tissues. Acute pain is commonly thought to last up to 7 days, but prolongation up to 30 days is common. Acute pain is often, but not always, associated with objective physical signs of autonomic nervous system activity (e.g., increased heart rate).
- *Chronic (persistent) pain:* Chronic pain is pain that persists beyond the time of healing.[8] The length of time is determined by the nature of the injury or surgical operation, but the pain is considered to be chronic (persistent) when it exceeds 3 months in duration.
- *Pain management:* Pain management is the clinical practice of relieving acute, subacute, and chronic (persistent) pain through the implementation of psychological, physical therapeutic, pharmacologic, and interventional methods. Physicians and pain psychologists practice pain management in a team model with the assistance of advanced practice providers and physical therapists in the inpatient and outpatient settings (also see Chapter 44).

Pain Services

- *Perioperative (acute) pain medicine service:* The perioperative pain medicine service is a team of highly specialized members who practice acute pain medicine and regional analgesic interventions for the patient who is about to have surgery, undergoing surgery, and in the process of recovery from surgery, and for trauma-induced pain. The role of the perioperative pain physician is to reduce the pain resulting from surgery and minimize the period of recuperation, and to inhibit the development of chronic (persistent) pain through early intervention. This service is most commonly found in the inpatient setting but crossover to the outpatient setting is expected for continuity of care.
- *Chronic (persistent) pain medicine service:* The chronic pain medicine service is a multidisciplinary team of providers who treat chronic (persistent) pain and cancer pain using diverse treatment modalities including psychological interventions, analgesic medications, and regional analgesic and chronic pain procedural interventions. The patient population served includes the perioperative patient with preoperative chronic/persistent pain issues, the inoperable patient with chronic/persistent pain issues, and patients who have not undergone surgery but have comorbid persistent pain. The role of the inpatient chronic pain physician is to attenuate the patient's pain, provide rationalized pain medication care, and transition the patient to outpatient pain care. The diagnosis and treatment of chronic pain is most commonly and most successfully performed in the outpatient setting, not in the acute care inpatient setting (also see Chapter 44).

NEUROBIOLOGY OF PAIN

Nociception

Nociception involves the recognition and transmission of painful stimuli. Stimuli generated from thermal, mechanical, or chemical tissue damage may activate nociceptors, which are free afferent nerve endings of myelinated Aδ and unmyelinated C fibers. These peripheral afferent nerve endings send axonal projections into the dorsal horn of the spinal cord, where they synapse with second-order afferent neurons. Axonal projections of second-order neurons cross to the contralateral side of the spinal cord, and ascend as afferent sensory pathways (e.g., spinothalamic tract) to the level of the thalamus.[9] Along the way, these neurons divide and send axonal projections to the reticular formation and periaqueductal gray matter. In the thalamus, second-order neurons synapse with third-order neurons, which send axonal projections into the sensory cortex.

Modulation of Nociception

Surgical incision produces tissue injury, with consequent release of histamine and inflammatory mediators, such as peptides (e.g., bradykinin), lipids (e.g., prostaglandins), neurotransmitters (e.g., serotonin), and neurotrophins (e.g., nerve growth factor).[10] The release of inflammatory mediators activates peripheral nociceptors, which initiate transduction and transmission of nociceptive information to the central nervous system (CNS). Noxious stimuli are transduced by peripheral nociceptors and transmitted by Aδ and C nerve fibers from peripheral visceral and somatic sites to the dorsal horn of the spinal cord, where integration of peripheral nociceptive and descending inhibitory modulatory input (i.e., serotonin, norepinephrine, γ-aminobutyric acid [GABA], and enkephalin) or descending facilitatory input (i.e., cholecystokinin, excitatory amino acids, dynorphin) occurs. Further transmission of nociceptive information is determined by complex modulating influences in the spinal cord. Some impulses pass to the ventral and ventrolateral horns to initiate spinal reflex responses. These segmental responses may include increased skeletal muscle tone, inhibition of phrenic nerve function, or even decreased gastrointestinal motility. Other signals are transmitted to higher centers through the spinothalamic and spinoreticular tracts, where they produce cortical responses to ultimately generate the perception of pain.

The question of how the disease of chronic pain develops from the symptom of acute pain remains unanswered. The traditional dichotomy between acute and chronic pain is somewhat arbitrary, as animal and clinical studies demonstrate that acute pain may become chronic pain. The duration of painful or noxious stimuli, type of stimuli, genetic or phenotypic makeup, or other possible factors that lead to the transition from the symptom of acute pain to the disease of chronic pain remain unclear.

Noxious stimuli can produce expression of new genes (the basis for neuronal sensitization) in the dorsal horn of the spinal cord within 1 hour, and these changes are sufficient to alter behavior within the same time frame.[11,12] Also, the intensity of acute postoperative pain is a significant predictor of chronic postoperative pain.[7] Continuous release of inflammatory mediators in the periphery sensitizes functional nociceptors and activates dormant nociceptors (Box 40.2).[6] Sensitization of peripheral nociceptors results in a decreased threshold for activation, increased discharge rate with activation, and increased rate of spontaneous discharge. Intense noxious input from the periphery may also produce central sensitization and hyperexcitability. Central sensitization is the development of "persistent post-injury changes in the CNS that result in pain hypersensitivity."[13] Hyperexcitability is the "exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage."[13]

Box 40.2 Endogenous Mediators of Inflammation

Prostaglandins ($PGE_1 > PGE_2$)
Histamine
Bradykinin
Serotonin
Acetylcholine
Lactic acid
Hydrogen ions
Potassium ions

PGE_1, *PGE_2*, Prostaglandins E_1 and E_2.

Box 40.3 Examples of Pain-Modulating Neurotransmitters

Excitatory
Glutamate
Aspartate
Vasoactive intestinal polypeptide
Cholecystokinin
Gastrin-releasing peptide
Angiotensin
Substance P

Inhibitory
Enkephalins
Endorphins
Somatostatin

Noxious input can trigger the cascade that leads to functional changes in the dorsal horn of the spinal cord and other sequelae. Ultimately, these changes may later cause postoperative pain to be perceived as more painful than would otherwise have been experienced. The neural circuitry in the dorsal horn is extremely complex, and we are just at the beginning of understanding the specific role of the various neurotransmitters and receptors in the process of nociception.[10,12]

Key receptors (e.g., *N*-methyl-D-aspartate [NMDA]) may play a significant role in the development of chronic pain after an acute injury. Neurotransmitters or second messenger effectors (e.g., substance P, protein kinase C-γ) may also play important roles in spinal cord sensitization and chronic pain (Box 40.3).[11] Our understanding of the neurobiology of nociception includes the dynamic integration and modulation of nociceptive transmission at several levels. Still, the specific roles of various receptors, neurotransmitters, and molecular structures in the process of nociception are not fully understood.

Preemptive and Preventive Analgesia

The development of central or peripheral sensitization after traumatic injury or surgical incision can result in amplification of postoperative pain. Therefore, preventing the establishment of altered central processing by analgesic treatment may, in the short term, reduce postprocedural or traumatic pain and accelerate recovery. In the long term, the benefits may include a reduction in chronic pain and improvement in the patient's quality of recovery and life satisfaction. Although the concept of preemptive analgesia in decreasing postinjury pain is valid, clinical trials are difficult to objectively conduct, which partly accounts for inconsistent conclusions.[14-16]

The precise definition of preemptive analgesia is one of the major controversies in perioperative pain medicine, and this lack of precision contributes to the confusion regarding its clinical relevance. Preemptive analgesia can be defined as an analgesic intervention initiated before the noxious stimulus develops in order to block peripheral and central pain transmission. Preventive analgesia can be functionally defined as an attempt to block pain transmission prior to the injury (incision), during the noxious insult (surgery itself), *and* after the injury and throughout the recovery period. Unfortunately, the concept of preventive analgesia has not been examined in a rigorous fashion. Confining the definition of preemptive analgesia to only the immediate preoperative or early intraoperative (incisional) period may not be clinically relevant or appropriate because the inflammatory response may last well into the postoperative period and continue to maintain peripheral sensitization. However, preventive analgesia is a clinically relevant phenomenon. Katz and McCartney[4] described an analgesic benefit of preventive analgesia but no such benefit with the preemptive strategy. Maximal clinical benefit is observed when there is complete blockade of noxious stimuli, with extension of this blockade into the postoperative period. Central sensitization and persistent pain after surgical incision are predominantly maintained by the incoming barrage of sensitized peripheral pain fibers throughout the perioperative period,[17] extending into the postsurgical recovery period. By avoiding central sensitization and its prolongation by peripheral input, preventive analgesia along with intensive multimodal analgesic interventions could, theoretically, reduce acute postprocedure pain/hyperalgesia and, therefore, chronic pain after surgery.[7]

Opioid-Induced Hyperalgesia

Short-term administration of opioids in the perioperative setting may unfortunately lead to opioid-induced hyperalgesia (OIH), a paradoxical increase in the patient's pain severity and decrease in pain tolerance. This has been demonstrated in humans who received intraoperative opioid infusion for operative analgesia as well as in human and animal experimental models.[18] Although the clinical impact of OIH has not been fully elucidated, the possibility of it contributing to acute postoperative pain should be considered. OIH has also

been implicated as a risk for the development of CPSP and the pronociceptive process involves the activation of the NMDA receptor.[18]

Multimodal Approach to Perioperative Recovery

A multimodal approach to analgesia is a broad definition that may include a combination of interventional analgesic techniques (epidural catheter or peripheral nerve catheter analgesia) and a combination of systemic pharmacologic therapies (nonsteroidal antiinflammatory drugs [NSAIDs], α-adrenergic agonists, NMDA receptor antagonists, membrane stabilizers, and opioid administration) (also see Chapters 9 and 17). Postprocedural or posttraumatic pain is best managed through this multimodal approach.[19] For instance, basic perioperative therapy, such as including a single dose of the membrane stabilizer, gabapentin, can attenuate postoperative pain and decrease opioid dosage with minimal side effects in various types of surgeries.[20]

The principles of a multimodal strategy include a sufficient improvement of the patient's pain to instill a sense of control over the pain, enable early mobilization, allow early enteral nutrition, and attenuate the perioperative stress response. The secondary goal of this approach is to maximize the benefit (analgesia) while minimizing the risk (i.e., side effects of the medication being used). These goals are often achieved through regional anesthetic techniques (also see Chapters 17 and 18) and a combination of analgesic drugs (also see Chapters 9 and 10). Epidural anesthesia and analgesia form an integral part of the multimodal strategy because of the superior analgesia and physiologic benefits conferred by epidural analgesia.[21] A multimodal approach involving a combination of neuraxial analgesia and systemic analgesics during recovery from radical prostatectomy resulted in a reduction of opioid use, lower pain scores, and decreased length of hospital stay.[22] Patients undergoing major abdominal or thoracic procedures and managed with a multimodal strategy have a reduction in hormonal and metabolic stress, preservation of total-body protein, shorter times to tracheal extubation, lower pain scores, earlier return of bowel function, and earlier attainment of criteria for discharge from the intensive care unit.[23] Integrating the most recent data and techniques for surgery, anesthesiology, and pain treatment, the multimodal approach is an extension of clinical pathways or fast track protocols by revamping traditional care programs into effective postoperative rehabilitation pathways.[23] This approach may potentially decrease perioperative morbidity, decrease the length of hospital stay, and improve patient satisfaction without compromising safety. However, the widespread implementation of these programs requires multidisciplinary collaboration, changes in the traditional principles of postoperative care, additional resources, and expansion of the traditional acute pain service, all of which may be challenging in the current medical economic climate.

ANALGESIC DELIVERY SYSTEMS

The traditional delivery systems for the management of perioperative pain have oral and parenteral on-demand administration of analgesics. More efficacious mechanisms, such as patient-controlled analgesia (PCA), are increasingly being used. A PCA mechanism can refer to oral, parenteral, neuraxial, or peripheral administration of an analgesic (Tables 40.1 to 40.3). This medication delivery technique is based on improved understanding of the neurobiology of pain and the potential deleterious effects of postoperative pain. The formation of perioperative pain management services, directed by anesthesiologists with expertise in the pharmacology of analgesics and regional analgesia, has facilitated the widespread application of these techniques and improved the care of the postoperative patient.

Patient-Controlled Analgesia

PCA can be delivered via oral, intravenous, subcutaneous, epidural, and intrathecal routes, as well as by peripheral nerve catheter. Upon activation of the delivery system, limits are placed on the number of doses per unit of time that will be administered to the patient. There is also a minimum time interval that must elapse between dose administrations (lockout interval). Also, a continuous background infusion superimposed on patient-controlled boluses can be implemented. Most patients determine a level of pain that is acceptable and taper their dosage requirements as they recover. Patients usually accept PCA because it restores their feeling of having control of their therapy. When compared with traditional methods of intermittent intramuscular or intravenous injections of opioids to manage perioperative pain, PCA provides better analgesia with more safety, less total drug use, less sedation, fewer nocturnal sleep disturbances, and more rapid return to physical activity.[24] Some institutions employ pulse oximetry monitoring to assess the respiratory depression associated with opioid administration. Although pulse oximetry is better than having no specific monitor at all, it may not capture the relationship between respiratory depression and opioid administration. The addition of supplemental oxygen lowers the detection sensitivity of pulse oximetry as a monitor for respiratory depression and renders this monitor ineffective. Capnography and respiratory rate are more specific monitors of respiratory depression. However, capnography is not readily available in all institutions and is not needed universally for patients receiving opioid therapy. Capnography is best reserved for patients with substantial

Table 40.1 Oral and Parenteral Analgesics for Treatment of Perioperative Pain

Agent	Route of Administration	Dose (mg)	Half-Life (h)	Onset (h)	Analgesic Action (h)	Peak Duration (h)
Opioids and Opioid Derivatives						
Morphine	Intravenous	2.5-15	2-3.5	0.25	0.125	2-3
	Intramuscular	10-15	3	0.3	0.5-1.5	3-4
	Oral	30-60	3	0.5-1	1-2	4
Codeine[a]	Oral	15-60	4	0.25-1	0.5-2	3-4
Hydromorphone	Intravenous	0.2-1.0	2-3	0.2-0.25	0.25	2-3
	Intramuscular	1-4	2-3	0.3-0.5	1	2-3
	Oral	1-4	2-3	0.5-1	1	3-4
Fentanyl	Intravenous	20-50 μg	0.5-1	5-10 min	5 min	1-1.5
	Transmucosal[b]	200-1600 μg	2-12	0.1-0.25	0.5-1	0.25-0.5
	Transdermal	12.5-100 μg	20-27	12-24	20-72	72
Oxymorphone	Oral	5-10	3.3-4.5	0.5	1	2-6
	Intravenous	0.5-1	3-5	0.15	0.25	3-6
	Subcutaneous	1-1.5	3-5	0.15	0.25	3-6
	Intramuscular	1-1.5	3-5	0.15	0.25	3-6
Hydrocodone	Oral	5-7.5	2-3	30	90	3-4
Oxycodone	Oral	5	3-5	0.5	1-2	4-6
Methadone	Oral	2.5-10	3-4	0.5-1	1.5-2	4-8
Propoxyphene	Oral	32-65	12-16	0.25-1	1-2	3-6
Other						
Tramadol[c]	Oral	50-100	5-6	0.5-1	1-2	4-6

[a]Not recommended for postoperative analgesia due to genetic variable metabolism.
[b]Transmucosal fentanyl is most appropriately reserved for breakthrough malignant (cancer) pain.
[c]Not classified by the U.S. Food and Drug Administration (FDA) as an opioid; however, tramadol possesses naloxone partial-reversal analgesia.

comorbid conditions that increase the risks associated with opioid therapy. Perhaps monitors that directly display respiratory rate with sufficient sensitivity and specificity will soon be available.

SYSTEMIC THERAPY

Oral Administration

Oral administration of analgesics is not optimal for the management of moderate to severe perioperative pain, primarily because of the nil per os (NPO, nothing by mouth) status of patients in the immediate postoperative period. Traditionally, postoperative patients are switched to oral analgesics (aspirin, acetaminophen, cyclooxygenase [COX-1/COX-2] inhibitors, opioids) when pain has diminished enough to eliminate the need for rapid adjustments of analgesia level.

Perioperative administration of opioid and nonopioid analgesic medications is an integral component of multimodal analgesic treatment plans. The increased complexity of outpatient surgical procedures has introduced the need for perioperative analgesia plans that enable moderate to severe postoperative pain to be effectively treated in the outpatient setting. Membrane stabilizers (gabapentin and pregabalin) used in the pre- and postoperative settings decrease postoperative pain and opioid consumption.[20,25] The optimal dose of gabapentin is 900 mg or more preoperatively followed by 400 to 600 mg three times a day postoperatively for 14 days; 300 mg of pregabalin followed by 150 mg two times a day should be given for maximal benefit. These drugs may provide postoperative pain relief but also may reduce CPSP.[26] NSAIDs including COX-2 predominant medications are effective when given intraoperatively and postoperatively but have not been found to have significant impact when given

Table 40.2 Guidelines for Delivery Systems Used in Intravenous Patient-Controlled Analgesia

Drug Concentration	Size of Bolus[a]	Lockout Interval (min)	Continuous Infusion
Agonists			
Morphine (1 mg/mL)	0.5-2.5 mg	6-10	1-2 mg/h
Fentanyl (0.01 mg/mL)	20-50 µg	5-10	10-100 µg/h
Hydromorphone (0.2 mg/mL)	0.05-0.25 mg	10-20	0.2-0.4 mg/h
Alfentanil (0.1 mg/mL)	0.1-0.2 mg	5-10	—
Methadone (1 mg/mL)	0.5-1.5 mg	10-30	—
Oxymorphone (0.25 mg/mL)	0.2-0.4 mg	8-10	—
Sufentanil (0.002 mg/mL)	2-5 µg	4-10	2-8 µg/h
Agonists-Antagonists			
Buprenorphine (0.03 mg/mL)	0.03-0.1 mg	8-20	—
Nalbuphine (1 mg/mL)	1-5 mg	5-15	—
Pentazocine (10 mg/mL)	5-30 mg	5-15	—

[a]All doses are for a 70-kg adult patient. The anesthesia provider should proceed with titrated intravenous loading doses if necessary to establish initial analgesia. Individual patient's requirements vary widely, with smaller doses typically given for elderly or compromised patients. Continuous infusions are not recommended for opioid-naïve adult patients. Continuous opioid infusion doses often are considerably higher in the cancer pain population.
Modified from Hurley RW, Murphy JD, Wu CL. Acute postoperative pain. In Miller RD, Cohen NH, Eriksson LI, et al, eds. *Miller's Anesthesia*. 8th ed. Philadelphia: Elsevier Saunders; 2015:2974-2998.

Table 40.3 Neuraxial Analgesics

Drug	Intrathecal or Subarachnoid Single Dose	Epidural Single Dose	Epidural Continuous Infusion
Opioid[a]			
Fentanyl	5-25 µg	50-100 µg	25-100 µg/h
Sufentanil	2-10 µg	10-50 µg	10-20 µg/h
Alfentanil	—	0.5-1 mg	0.2 mg/h
Morphine	0.1-0.3 mg	1-5 mg	0.1-1 mg/h
Hydromorphone	—	0.5-1 mg	0.1-0.2 mg/h
Extended-release morphine[†]	Not recommended	5-15 mg	Not recommended
Local Anesthetic[b]			
Bupivacaine	5-15 mg	25-150 mg	1-25 mg/h
Ropivacaine	Not recommended	25-200 mg	6-20 mg/h
Adjuvant Medications			
Clonidine	Not recommended	100-900 µg	10-50 µg/h

[a]Doses are based on use of a neuraxial opioid alone. No continuous intrathecal or subarachnoid infusions are provided. Smaller doses may be effective when administered to the elderly or when injected in the cervical or thoracic region. Units vary across drugs for single dose (mg versus µg) and continuous infusion (mg/h versus µg/h).
[b]Most commonly used in combination with an opioid, in which case the total dose of local anesthetic is reduced.
Modified from Hurley RW, Murphy JD, Wu CL. Acute postoperative pain. In Miller RD, Cohen NH, Eriksson LI, et al, eds. *Miller's Anesthesia*. 8th ed. Philadelphia: Elsevier Saunders; 2015:2974-2998.

alone and preoperatively. However, they are effective for acute postsurgical pain and CPSP when given as part of a preoperative polypharmacologic regimen including gabapentinoids. Preoperative administration of acetaminophen may improve acute postoperative pain but has not been shown to reduce CPSP. Amine reuptake inhibitors such as tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors have not received sufficient investigation to draw conclusions about their efficacy in acute postoperative pain or the prevention of CPSP. Preoperative doses of vitamin C may reduce the incidence of complex regional pain syndrome following orthopedic extremity surgery although the quality of evidence is not strong.[27]

Intravenous Administration

Intermittent intravenous (IV) administration of small doses of opioids (see Tables 40.1 and 40.2) is commonly used to treat acute and severe pain in the PACU or intensive care unit, where continuous nursing surveillance and monitoring are available. With a small intravenous dose of an opioid, the time delay for analgesia and the variability in plasma concentrations characteristic of intramuscular injections are minimized. Rapid redistribution of the opioid produces a shorter duration of analgesia after a single intravenous administration than after an intramuscular injection.

Ketamine is traditionally recognized as an intraoperative anesthetic; however, it is also effective in small dose (subanesthetic or analgesic dose, up to 15 μg/kg/min) infusions for postoperative analgesia partly because of its direct analgesic properties through antagonism of the NMDA receptor. It has also been shown to reduce the OIH associated with intraoperative opioid infusion.[18] Patients receiving large doses of opioids may experience hyperalgesia, resulting in increased excitatory amino acid release in the spinal cord. Ketamine directly inhibits the actions of the excitatory amino acids and reverses OIH, leading to improved postoperative pain outcome. Microdosing of ketamine (2 μg/kg/min) was ineffective for either postoperative pain or CPSP. Preoperative intravenous ketamine bolus dose of 0.5 mg/kg followed by an intraoperative infusion of a subanesthetic dose (4 to 5 μg/kg/min) of ketamine reduces postoperative pain and CPSP. This indirect antihyperalgesic effect may occur through suppression of central sensitization.[28] The benefit of subanesthetic dosing of ketamine also includes a decrease in postoperative nausea and vomiting, with minimal adverse effects. Subanesthetic ketamine infusions do not cause hallucinations or cognitive impairment. The incidence of side effects, such as dizziness, itching, nausea, or vomiting, is comparable to that seen with opioids. Therefore, the use of perioperative ketamine in patients at high risk for the development of CPSP is warranted.

Acetaminophen can be given intravenously in addition to orally and rectally. This has increased the ability to provide additional nonopioid analgesia to patients who are NPO but refuse rectal administration. Despite patient, and often provider, assumptions that intravenous preparations are more potent or effective, no clinical trial has demonstrated a difference in efficacy between oral and intravenous formulations.[29] Although the formulations differ in bioavailability and time to onset of analgesia, intravenous dosing has not been associated with improved efficacy.

Preoperative administration of dexamethasone decreases acute postoperative pain scores and decreases opioid consumption on a dose-dependent basis when more than 10 mg are given.[30] Intraoperative administration of clonidine decreases postoperative pain, but bradycardia and hypotension limit the benefits of its modest analgesic properties. Intraoperative magnesium administration reduces postoperative pain and opioid requirements.[31] The mechanism of action is likely the increased blockade of the NMDA receptor.

Subcutaneous Administration

Subcutaneous administration of select medications (hydromorphone) is highly efficacious and is a very practical approach for providing analgesia in patients without intravenous access or those in need of long-term, home-based analgesic care. The administration of hydromorphone exerts basically the same pharmacokinetics whether it is administered subcutaneously or intravenously. This modality is primarily used in palliative care populations.

Transdermal/Iontophoretic Administration

The development of iontophoretic fentanyl and the validation of its efficacy in postoperative patients may expand the possibilities of parenteral administration. However, because the intramuscular or subcutaneous route possesses a rapid onset time, it may be the best alternative for patients who are without immediate intravenous access.

Transmucosal Administration

Transmucosal delivery of analgesics, such as fentanyl, may serve as an alternative to the oral administration of NSAIDs and opioids, especially when a rapid onset of drug effect is desirable. However, these medications rarely have a role in the management of postoperative pain because intravenous, intramuscular, subcutaneous, and oral delivery routes are usually sufficient for the delivery of analgesic medications.

NEURAXIAL ANALGESIA

A variety of neuraxial (intrathecal and epidural) and peripheral regional analgesic techniques are employed for postoperative pain. In general, when compared to

systemic opioids, epidural and peripheral techniques can provide superior analgesia, especially when local anesthetics are applied; furthermore, these techniques may decrease morbidity and mortality rates.[32] Clinical judgment is important with regard to the concerns regarding the use of these techniques in the presence of various anticoagulants (see later discussion; also see Chapter 17).

Intrathecal Administration

Intrathecal administration of an opioid can provide short-term to intermediate length postoperative analgesia after a single injection. The intrathecal route offers the advantage of precise and reliable placement of small concentrations of the drug near its site of action. The onset of analgesic effects after intrathecal administration of an opioid is directly proportional to the lipid solubility of the drug. Duration of effect is longer with more hydrophilic compounds. Morphine produces peak analgesic effects in 20 to 60 minutes and postoperative analgesia for 12 to 36 hours. Adding a small dose of fentanyl to the morphine-containing opioid solution may speed the onset of analgesic effect. For lower abdominal surgical procedures performed with spinal anesthesia (cesarean section, transurethral resection of the prostate), morphine may be added to the local anesthetic solution to increase the duration of analgesia.

The primary disadvantage of an intrathecal opioid injection is the lack of flexibility inherent to a single-shot modality. Clinicians must either repeat the injection or consider other options when the analgesic effect of the initial dose diminishes. The practical aspects of leaving a catheter in the intrathecal space for either continuous or repeated intermittent opioid injections is controversial, especially in view of reports of cauda equina syndrome after continuous spinal anesthesia with hyperbaric local anesthetic solutions injected through a small-diameter catheter.

Epidural Administration

Epidural administration of a local anesthetic as a continuous infusion through an epidural catheter is a common method of providing perioperative analgesia (also see Chapter 17). Epidural infusions of local anesthetic alone may be used for postoperative analgesia but usually are not as effective in controlling pain as local anesthetic-opioid epidural analgesic combinations. This is due to the significant failure rate (from regression of sensory block and inadequate analgesia) and relatively high incidence of motor block and hypotension. Epidural infusions of local anesthetic alone may be warranted for postoperative analgesia, with the goal of avoiding opioid-related side effects.

The benefit of opioid monotherapy in epidural infusions is that they generally do not cause motor block or hypotension from sympathetic blockade. There are mechanistic differences between continuous epidural infusions of lipophilic (e.g., fentanyl, sufentanil) and hydrophilic (e.g., morphine, hydromorphone) opioids. The analgesic site of action (spinal versus systemic) for continuous epidural infusions of lipophilic opioids is not clear, although several randomized clinical trials suggest that it is systemic[33] because there were no differences in plasma concentrations, side effects, or pain scores between those who received intravenous and those who received epidural infusions of fentanyl. A continuous infusion, rather than an intermittent bolus of epidural opioids, may provide superior analgesia with fewer side effects. Hydrophilic opioid epidural infusions have a spinal mechanism of action. The impact of epidural analgesia is dependent upon the total dose administered rather than the volume or concentration; therefore, a larger concentration of local anesthetic delivered in a small volume is functionally equivalent to that of a small concentration in a larger volume.

Epidural analgesia (local anesthetic with and without opioids) for abdominal surgeries provides superior pain relief in the initial postoperative period, with fewer gastrointestinal-related side effects compared to systemic opioid therapy; however, pruritus often occurs. Epidural analgesia is beneficial for major joint surgery of the lower extremity but has the associated disadvantages of neuraxial analgesia. Thoracic epidural analgesia has been the mainstay of analgesia for thoracotomy, but paravertebral blockades may be just as effective with a more favorable side effect profile.[34] One of the primary benefits of epidural analgesia for traumatic rib fractures is the decreased duration of mechanical ventilation required when compared to using a local anesthetic alone.

Side Effects of Neuraxial Analgesic Drugs

Many medication-related (opioid and local anesthetic) side effects can occur with postoperative epidural analgesia. When side effects are suspected, the patient's overall clinical status should be evaluated so that serious comorbid conditions are not inappropriately attributed to epidural analgesia. The differential diagnosis for a patient with neuraxial analgesia and hypotension should also include hypovolemia, bleeding, and a decreased cardiac output. Patients with respiratory depression should also be evaluated for cerebrovascular accident, pulmonary edema, and evolving sepsis. Standing orders and nursing protocols for analgesic regimens, neurologic monitoring, treatment of side effects, and physician notification about critical variables should be standard for all patients receiving neuraxial and other types of postoperative analgesia.

Most Common Side Effects

The most frequent side effects of neuraxial analgesia include the following:

- *Hypotension* (0.3% to 7%)—Local anesthetics used in an epidural analgesic regimen may block sympathetic fibers and contribute to postoperative hypotension.
- *Motor block* (2% to 3%)—In most cases, motor block resolves within 2 hours after discontinuing the epidural infusion. Persistent or increasing motor block should be promptly evaluated, and spinal hematoma, spinal abscess, and intrathecal catheter migration should be considered as part of the differential diagnosis.
- *Nausea, vomiting, and pruritus* (15% to 18%)—Pruritus is one of the most common side effects of epidural or intrathecal administration of opioids, with an incidence of approximately 60% compared with about 15% to 18% for local epidural anesthetic administration or systemic opioids.
- *Respiratory depression* (0.1% to 0.9%)—Neuraxial opioids administered in appropriate doses are not associated with a higher incidence of respiratory depression than that seen with systemic administration of opioids. Risk factors for respiratory depression with neuraxial opioids include larger dose, geriatric age group, concomitant administration of systemic opioids or sedatives, the possibility of prolonged or extensive surgery, the presence of comorbid conditions, and thoracic surgery.
- *Urinary retention* (10% to 30%)—Epidural administration of local anesthetics and opioids is associated with urinary retention.

Anticoagulation

The concurrent use of anticoagulants with neuraxial anesthesia and analgesia has always been a relatively controversial issue. However, the introduction of low-molecular-weight heparin in North America in 1993 increased the incidence of spinal hematomas. Traditionally, the incidence of spinal hematoma is estimated at approximately 1 in 150,000 for epidural block, with a lower incidence of 1 in 220,000 for spinal blocks.[35] Before its introduction in North America, low-molecular-weight heparin was used in Europe without significant problems. However, the incidence of spinal hematoma increased to as high as 1 in 40,800 for spinal anesthetics and 1 in 6600 for epidural anesthetics (1 in 3100 for postoperative epidural analgesia) in the United States between 1993 and 1998. The estimate of the higher incidence of spinal hematomas after epidural catheter removal is based in part on the Food and Drug Administration MedWatch data, which suggest that epidural catheter removal may be a traumatic event, although this is still a relatively controversial issue.

Different types and classes of anticoagulants vary in pharmacokinetic properties that affect the timing of neuraxial catheter or needle insertion and catheter removal. Despite a number of observational and retrospective studies investigating the incidence of spinal hematoma in the setting of various anticoagulants and neuraxial techniques, there is no definitive conclusion regarding the absolute safety of neuraxial anesthesia and anticoagulation. The American Society of Regional Anesthesia and Pain Medicine (ASRA) lists a series of consensus statements, based on the available literature, for the administration (insertion and removal) of neuraxial techniques in the presence of various anticoagulants, including oral anticoagulants (warfarin), antiplatelet agents, fibrinolytics-thrombolytics, standard unfractionated heparin, and low-molecular-weight heparin. The ASRA consensus statements include the concepts that (1) the timing of neuraxial needle or catheter insertion or removal should reflect the pharmacokinetic properties of the specific anticoagulant; (2) frequent neurologic monitoring is essential; (3) concurrent administration of multiple anticoagulants may increase the risk of bleeding; and (4) the analgesic regimen should be tailored to facilitate neurologic monitoring, which may be continued in some cases for 24 hours after epidural catheter removal. An updated version of the ASRA consensus statements on neuraxial anesthesia and anticoagulation[36] can be found on their website,[36] with some of these statements addressing the newer anticoagulants (also see Chapter 13).

Infection

Infection associated with postoperative epidural analgesia may result from exogenous or endogenous sources. Serious infections (e.g., meningitis, spinal abscess) associated with epidural analgesia are rare (<1 in 10,000), although some researchers report a higher incidence (approximately 1 in 1000 to 1 in 2000).[37] Closer examination of the studies that report a higher incidence of epidural abscesses reveal that the patients had a relatively longer duration of epidural analgesia or the presence of coexisting immunocompromising or complicating diseases (e.g., malignancy, trauma). Use of epidural analgesia in the general surgical population, with a typical duration of postoperative catheterization of approximately 2 to 4 days, is generally not associated with epidural abscess formation. A trial of postoperative epidural analgesia (mean catheterization of 6.3 days) in more than 4000 surgical cancer patients did not reveal any abscesses.

SURGICAL SITE (INCISION) INFILTRATION

Surgical site infiltration with local anesthetic prior to incision and prior to tissue closure is recommended for the reduction of postoperative pain.[38] Liposomal bupivacaine (EXPAREL, Pacira Pharmaceuticals) was approved in 2011 for surgical site administration following bunionectomy and hemorrhoidectomy. Although this extended release

formulation is designed to slowly release bupivacaine to surrounding tissues over 96 hours, it was superior to placebo only for the first 24 hours after administration.[39]

INTRA-ARTICULAR ADMINISTRATION

Intra-articular injection of opioids may provide analgesia for up to 24 hours postoperatively and prevent the development of chronic postsurgical pain. Opioid receptors are found in the peripheral terminals of primary afferent nerves, which may explain this improved analgesia, despite the lack of response with the addition of opioids to perineural anesthetic injections. The analgesic benefit of intra-articular opioids over systemic administration has not been demonstrated, and the systemic analgesic effect of these injections has not been excluded. Extended-release bupivacaine was found to be less effective than traditional local anesthetic and opioid infiltration in one study and no different from traditional bupivacaine alone in another.[39] Glenohumeral intra-articular continuous catheters have been associated with chondrolysis when bupivacaine is used and therefore should be avoided.[40]

INTRAPLEURAL ANALGESIA

Intrapleural regional analgesia is produced by the injection of a local anesthetic solution through a catheter inserted percutaneously into the intrapleural space. The local anesthetic diffuses across the parietal pleura to the intercostal neurovascular bundle and produces a unilateral intercostal nerve block at multiple levels. Effective postoperative pain relief requires intermittent intrapleural injections approximately every 6 hours of large volumes of local anesthetic (20 mL of 0.25% to 0.5% bupivacaine). This large bolus of local anesthetic introduced into the intrapleural space produces significant side effects while providing minimal analgesia. Pleural drainage tubes placed after a thoracotomy will result in a large loss of the local anesthetic solution and, consequently, poor analgesia. This technique is recommended only if all other options have been exhausted.

PERIPHERAL NERVE BLOCK

Peripheral nerve blockade can provide analgesia as part of an autonomous or multimodal pain regimen. Single-shot injections can provide coverage for intraoperative pain control. However, many providers feel that the risk of the intervention warrants the prolonged benefit, which includes postoperative pain control, and have driven the need for flexible duration of action. Intermediate-term pain relief (<24 hours) can be achieved with a combination of a local anesthetic and adjuvant drugs in a single injection. Longer-acting pain control may be indicated by the surgical technique, rehabilitation needs, and patient comorbid conditions and can be achieved by utilizing perineural catheters for continuous local anesthetic infusions.

Techniques

Nerve blocks can be inserted using anatomic landmarks, nerve stimulation, and ultrasound guidance. The efficacy between ultrasound-guided techniques and nerve stimulation varies, depending on the skill of the provider, primarily resulting in differences in comfort during placement and procedural time of the blockade. Nonetheless, these techniques provide a comparable quality of analgesia and similar complication profile.[43]

Adjuvant Drugs

Commonly used adjuvant drugs include epinephrine, clonidine, and opioids. Epinephrine for peripheral nerve blockade significantly increases the duration of the blockade, with minimal side effects. Epinephrine can also increase the sensitivity of intravascular injection; concentrations of 2.5 to 5 μg/mL are generally used. The mechanism of this effect is primarily through vasoconstriction. Opioids probably should not be added to a peripheral nerve blockade. Clonidine is beneficial in extending the duration of preoperative blockade but has less value with perineural catheters. The mechanism is most likely peripheral α_2-adrenergic receptor–mediated and dose-dependent. Clonidine is a better preemptive analgesic when added to a local anesthetic block than when used as a single drug. Side effects, including hypotension, bradycardia, and sedation, are less likely to occur with doses less than 1.5 μg/kg.[44] The use of clonidine increases the duration of analgesia and motor blockade by approximately 2 hours. More recently, the addition of dexmedetomidine to peripheral nerve blocks has been shown to improve analgesia duration and opioid reduction.[45]

REGIONAL ANALGESIA

Efficacy and safety are primary limiting factors in the implementation of any therapeutic measure. Regional analgesia is becoming an increasingly popular technique for perioperative pain control and has several specific advantages and disadvantages. The technical details of these blocks are covered in the regional anesthesia chapter; this section focuses on the utility and comparative efficacy of these blocks (also see Chapter 18).

Catheter Versus Single-Shot Techniques

Upper Extremity

Continuous interscalene blockade allows for longer duration of action compared with single-shot techniques.

This technique has increased utility with the posterior interscalene approach for moderate to severely painful shoulder surgeries. The continuous administration allows for increased pain relief, with minimal opioid supplementation and increased patient satisfaction and sleep quality.[46]

Lower Extremity

Lower extremity orthopedic surgeries resulting in moderate to severe perioperative pain also benefit from long-acting regional techniques. Lower extremity perineural catheters are utilized for major joint surgery of the hip, knee, ankle, and foot. This type of catheter may decrease clinical signs of inflammation for some lower extremity procedures, although inflammation is not decreased at the cellular level. Epidural catheters are utilized to provide good analgesia for major joint surgeries of the lower extremities, but expose patients to neuraxial analgesia risks, and generally have bilateral effects. Lumbar plexus catheters have been utilized as part of a multimodal regimen, with better pain scores at rest and with physical therapy than multimodal regimens that include PCA with or without femoral catheters for unilateral hip repairs.[47] Patients undergoing major foot and ankle surgeries under continuous perineural blockade are not only potentially able to obtain pain relief comparable to single-shot and systemic analgesia but also are discharged from PACUs in a shorter period of time.[48]

PARAVERTEBRAL BLOCKS

The increased utilization of paravertebral blockade can be directly correlated with the beneficial effects for patients undergoing breast surgery. This block provides an effective mechanism for controlling acute pain associated with this procedure, but has also demonstrated benefit in decreasing the development of chronic postsurgical pain over other analgesic regimens.[41] This technique can be performed as a single-shot technique or as a continuous catheter infusion to provide ongoing perioperative analgesia. This use of the technique has expanded to thoracic, cardiac, and pediatric applications.[42]

TRANSVERSUS ABDOMINIS PLANE BLOCK

Neuraxial analgesia techniques are starting to face competition from the transversus abdominis plane (TAP) block for many abdominal procedures. Theoretical advantages of this technique over other modalities include avoidance of both neuraxial involvement and lower extremity blockade, decreased urinary retention, and decreased systemic side effects. Compared with placebo blocks, TAP block provides increased analgesia and decreased systemic medication requirements as part of a multimodal analgesic regimen for total abdominal hysterectomy, cesarean section, and laparoscopic cholecystectomy. Moreover, guidance by ultrasound has made this a more reliably efficacious treatment modality.[49]

QUESTIONS OF THE DAY

1. How many organ systems are affected by acute postoperative pain? What are the adverse physiologic effects in each system?
2. What is the rationale for a multimodal approach to perioperative pain management? What medications and routes of delivery can be used as part of a multimodal analgesic plan?
3. What are the typical parameters that should be ordered for patient-controlled analgesia (PCA) with hydromorphone in an opioid-naïve patient?
4. A patient is receiving postoperative epidural analgesia with an infusion of ropivacaine and fentanyl. What side effects are most likely to occur? What are the risk factors for respiratory depression with neuraxial opioids?
5. What surgical procedures are most suitable for postoperative analgesia with a transversus abdominis plane (TAP) block?

REFERENCES

1. Buvanendran A, Fiala J, Patel KA, et al. The incidence and severity of postoperative pain following inpatient surgery. *Pain Med*. 2015;16:2277–2283.
2. Apfelbaum JL, Chen C, Mehta SS, et al. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth Analg*. 2003;97(2):534–540.
3. Wanderer JP, Shi Y, Schildcrout JS, et al. Supervising anesthesiologists cannot be effectively compared according to their patients' postanesthesia care unit admission pain scores. *Anesth Analg*. 2015;120(4):923–932.
4. Katz J, McCartney CJ. Current status of preemptive analgesia. *Curr Opin Anaesthesiol*. 2002;15(4):435–441.
5. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367(9522):1618–1625.
6. Carr DB, Goudas LC. Acute pain. *Lancet*. 1999;353(9169):2051–2058.
7. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. *Anesthesiology*. 2000;93(4):1123–1133.
8. Merskey H. Pain and psychological medicine. In: Wall PD, Melzack R, eds. *Textbook of Pain*. 3rd ed. New York: Churchill Livingstone; 1994:903–920.
9. Basbaum AI, Fields HL. Endogenous pain control systems: brainstem spinal pathways and endorphin circuitry. *Annu Rev Neurosci*. 1984;7:309–338.

10. Julius D, Basbaum AI. Molecular mechanisms of nociception. *Nature*. 2001;413(6852):203–210.
11. Basbaum AI. Spinal mechanisms of acute and persistent pain. *Reg Anesth Pain Med*. 1999;24(1):59–67.
12. Besson JM. The neurobiology of pain. *Lancet*. 1999;353(9164):1610–1615.
13. Kissin I. Preemptive analgesia. *Anesthesiology*. 2000;93(4):1138–1143.
14. Moiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. *Anesthesiology*. 2002;96(3):725–741.
15. Dahl JB, Moiniche S. Pre-emptive analgesia. *Br Med Bull*. 2004;71:13–27.
16. Ong CK, Lirk P, Seymour RA, et al. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesth Analg*. 2005;100(3):757–773.
17. Pogatzki-Zahn EM, Zahn PK. From preemptive to preventive analgesia. *Curr Opin Anaesthesiol*. 2006;19(5):551–555.
18. Joly V, Richebe P, Guignard B, et al. Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology*. 2005; 103(1):147–155.
19. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth*. 1997;78(5):606–617.
20. Hurley RW, Cohen SP, Williams KA, et al. The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. *Reg Anesth Pain Med*. 2006;31(3):237–247.
21. Block BM, Liu SS, Rowlingson AJ, et al. Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA*. 2003;290(18):2455–2463.
22. Ben-David B, Swanson J, Nelson JB, et al. Multimodal analgesia for radical prostatectomy provides better analgesia and shortens hospital stay. *J Clin Anesth*. 2007;19(4):264–268.
23. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg*. 2002;183(6):630–641.
24. Egbert AM, Parks LH, Short LM, et al. Randomized trial of postoperative patient-controlled analgesia vs intramuscular narcotics in frail elderly men. *Arch Intern Med*. 1990;150(9):1897–1903.
25. Elia N, Lysakowski C, Tramer MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. *Anesthesiology*. 2005;103(6):1296–1304.
26. Buvanendran A, Kroin JS, Della Valle CJ, et al. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. *Anesth Analg*. 2010;110(1):199–207.
27. Evaniew N, McCarthy C, Kleinlugtenbelt YV, et al. Vitamin C to prevent complex regional pain syndrome in patients with distal radius fractures: a meta-analysis of randomized controlled trials. *J Orthop Trauma*. 2015;29(8):e235–e241.
28. De Kock M, Lavand'homme P, Waterloos H. 'Balanced analgesia' in the perioperative period: is there a place for ketamine? *Pain*. 2001;92(3):373–380.
29. Jibril F, Sharaby S, Mohamed A, et al. Intravenous versus oral acetaminophen for pain: systematic review of current evidence to support clinical decision-making. *Can J Hosp Pharm*. 2015;68(3):238–247.
30. Nielsen RV, Siegel H, Fomsgaard J, et al. Preoperative dexamethasone reduces acute but not sustained pain after lumbar disc surgery: a randomized, blinded, placebo-controlled trial. *Pain*. 2015;156(12):2538–2544.
31. De Oliveira Jr GS, Castro-Alves LJ, Khan JH, et al. Perioperative systemic magnesium to minimize postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology*. 2013; 119(1):178–190.
32. Wu CL, Fleisher LA. Outcomes research in regional anesthesia and analgesia. *Anesth Analg*. 2000;91(5):1232–1242.
33. Loper KA, Ready LB, Downey M, et al. Epidural and intravenous fentanyl infusions are clinically equivalent after knee surgery. *Anesth Analg*. 1990;70(1):72–75.
34. Gulbahar G, Kocer B, Muratli SN, et al. A comparison of epidural and paravertebral catheterisation techniques in post-thoracotomy pain management. *Eur J Cardiothorac Surg*. 2010;37(2):467–472.
35. Tryba M. [Epidural regional anesthesia and low molecular heparin: Pro]. *Anasthesiol Intensivmed Notfallmed Schmerzther*. 1993;28(3):179–181.
36. Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med*. 2010;35(1):64–101. Also available at www.asra.com.
37. Horlocker TT, Wedel DJ. Neurologic complications of spinal and epidural anesthesia. *Reg Anesth Pain Med*. 2000;25(1):83–98.
38. Group TPW. PROSPECT (Procedure Specific Postoperative Pain Management). http://www.postoppain.org/; Accessed October, 1, 2015.
39. Uskova A, O'Connor JE. Liposomal bupivacaine for regional anesthesia. *Curr Opin Anaesthesiol*. 2015;28(5):593–597.
40. Busfield BT, Romero DM. Pain pump use after shoulder arthroscopy as a cause of glenohumeral chondrolysis. *Arthroscopy*. 2009;25(6):647–652.
41. Vila Jr H, Liu J, Kavasmaneck D. Paravertebral block: new benefits from an old procedure. *Curr Opin Anaesthesiol*. 2007;20(4):316–318.
42. Wardhan R. Update on paravertebral blocks. *Curr Opin Anaesthesiol*. 2015;28(5):588–592.
43. Fredrickson MJ, Ball CM, Dalgleish AJ, et al. A prospective randomized comparison of ultrasound and neurostimulation as needle end points for interscalene catheter placement. *Anesth Analg*. 2009;108(5):1695–1700.
44. Neal JM, Gerancher JC, Hebl JR, et al. Upper extremity regional anesthesia: essentials of our current understanding, 2008. *Reg Anesth Pain Med*. 2009;34(2):134–170.
45. Fritsch G, Danninger T, Allerberger K, et al. Dexmedetomidine added to ropivacaine extends the duration of interscalene brachial plexus blocks for elective shoulder surgery when compared with ropivacaine alone: a single-center, prospective, triple-blind, randomized controlled trial. *Reg Anesth Pain Med*. 2014;39(1):37–47.
46. Mariano ER, Afra R, Loland VJ, et al. Continuous interscalene brachial plexus block via an ultrasound-guided posterior approach: a randomized, triple-masked, placebo-controlled study. *Anesth Analg*. 2009;108(5):1688–1694.
47. Marino J, Russo J, Kenny M, et al. Continuous lumbar plexus block for postoperative pain control after total hip arthroplasty. A randomized controlled trial. *J Bone Joint Surg Am*. 2009;91(1):29–37.
48. Hunt KJ, Higgins TF, Carlston CV, et al. Continuous peripheral nerve blockade as postoperative analgesia for open treatment of calcaneal fractures. *J Orthop Trauma*. 2010;24(3):148–155.
49. El-Dawlatly A, Turkistani A, Kettner S, et al. Ultrasound-guided transversus abdominis plane block: description of a new technique and comparison with conventional systemic analgesia during laparoscopic cholecystectomy. *Br J Anaesth*. 2009;102(6):763–767.