Postoperative Pain Control

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KEYWORDS

• Postoperative pain • Multimodal analgesia • Opioids • Nerve blocks
• Local anesthetics

KEY POINTS

- Inadequate treatment of postoperative pain may lead to worse outcomes and persistent postoperative pain.
- A multimodal approach to pain management (including preemptive and preventative analgesia) lessens the dependence on any given medication and improves outcome.
- Local anesthetics can be administered via multiple routes (eg, wound infiltration, epidural, peripheral nerve blocks) to improve analgesia and decrease opioid requirements and opioid-related side effects.
- Despite multiple adverse effects, opioids remain the mainstay of surgical pain control.

INTRODUCTION

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1] Effective control and management of postoperative pain are clearly of primary concern to the patient and also of importance to the surgeon, because of potential adverse effects of the physiologic response to pain from surgery. Inadequate treatment of postoperative pain continues to be an important clinical problem, not only leading to worse outcomes in the immediate postoperative period but also an increased risk for persistent postoperative pain. Persistent postsurgical pain, pain that lasts beyond the typical healing period of 1 to 2 months, has become increasingly recognized as a significant issue after surgery and may exceed 30% after some operations, particularly amputations, thoracotomy, mastectomy, and inguinal hernia repairs.[2]

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Surg Clin N Am 95 (2015) 301–318
http://dx.doi.org/10.1016/j.suc.2014.10.002 **surgical.theclinics.com**
0039-6109/15/$ – see front matter

Inadequate pain relief occurs secondary to multiple factors, including insufficient knowledge of the care providers, fear of medication side effects, and inadequate patient preparation. Optimal management of postoperative pain requires an understanding of the pathophysiology of pain, methods used for assessment of pain in individual patients, and awareness of the various options available for pain control. Key factors to consider are type of surgical procedure, skills of the surgeon and anesthesiologist, concerns of the patient, and the experience and cooperation of nursing and other health care providers. Based on this foundation of understanding, use of a procedure-specific, multimodal perioperative pain management provides a rational basis for enhanced postoperative recovery and reduction of morbidity.[3–5]

PATHOPHYSIOLOGY OF POSTOPERATIVE PAIN

Acute postoperative pain is a normal response to surgical intervention and is a cause of delayed recovery and discharge after surgery as well as increased risk of wound infection and respiratory/cardiovascular complications.[6] Untreated acute pain leads to reduced patient satisfaction and increased morbidity and mortality and also places a burden on the patient and health system finances. Acute pain that becomes intractable and persists is referred to as chronic postsurgical pain (CPSP). CPSP can have a significant impact on the patient's quality of life and daily activities, including disturbances of sleep and affective mood.[2,6] Pain lasting more than 1 month after surgery occurs in 10% to 50% of individuals after common procedures, and 2% to 10% of these patients continue on to experience severe chronic pain.[7] Risk factors for the development of CPSP are outlined in **Box 1**.

Acute postsurgical pain occurs secondary to inflammation from tissue trauma or direct nerve injury and can be classified as nociceptive or neuropathic (**Table 1**). Tissue trauma releases local inflammatory mediators, which can produce hyperalgesia (increased sensitivity to stimuli in the area surrounding an injury) or allodynia (misperception of pain to nonnoxious stimuli). Other mechanisms contributing to hyperalgesia and allodynia include sensitization of the peripheral pain receptors (primary hyperalgesia) and increased excitability of central nervous system neurons (secondary hyperalgesia).[8]

It is increasingly recognized that genetic factors should be considered within the context of the interacting physiologic, psychological, and environmental factors that influence responses to pain and analgesia.[1] Genetic factors regulating opioid pharmacokinetics (metabolizing enzymes, transporters) and pharmacodynamics (receptors and signal transduction elements) contribute to a large interpatient variability in postoperative opioid requirements. Specific examples include genetic polymorphisms, which affect plasma concentrations of active metabolites of codeine and tramadol as well as plasma concentrations of methadone.[1]

Pain control has traditionally used opioid analgesia to target central mechanisms involved in the perception of pain. A multimodal approach recognizing the pathophysiology of surgical pain uses several agents to decrease pain receptor activity and diminish the local hormonal response to injury.[8,9] This approach lessens the dependence on a given medication and mechanism. For example, local anesthetics can directly block pain receptor activity, antiinflammatory agents can decrease the hormonal response to injury, and drugs such acetaminophen, ketamine, clonidine, dexmedetomidine, gabapentin, and pregabalin can produce analgesia by targeting specific neurotransmitters.[8] Nonopioid agents used for management of postoperative pain are outlined in **Table 2**.

Box 1
Risk factors for chronic postsurgical pain

- Pain, moderate to severe, lasting more than 1 month
- Repeat surgery
- Catastrophizing[a]
- Anxiety
- Female gender
- Younger age (adults)
- Workers' compensation
- Genetic predisposition
- Surgical approach with risk of nerve damage
- Moderate to severe postoperative pain
- Radiation therapy to area
- Neurotoxic chemotherapy
- Depression
- Neuroticism

[a] Refers to giving greater weight to the worst possible outcome, however unlikely, or experiencing a situation as unbearable or impossible when it is just uncomfortable.

Adapted from Macintyre PE, Scott DA, Schug SA, et al. Acute pain management: scientific evidence [Systematic reviews and meta-analyses]. 3rd edition. 2010. Available at: http://www.anzca.edu.au/resources/college-publications/pdfs/Acute%20Pain%20Management/books-and-publications/acutepain.pdf. Accessed June 25, 2014; and Kehlet H, Rathmell JP. Persistent postsurgical pain. Anesthesiology 2010;112:514–5.

Table 1
Types of pain

Nociceptive Pain	• Normal processing of stimuli that damages normal tissues • Responds to opioids
Somatic	• Pain arises from bone, joint, muscle, skin, or connective tissue • Aching, throbbing • Localized
Visceral	• Arises from visceral organs • Tumor: localized pain • Obstruction of hollow viscus: poorly localized
Neuropathic Pain	• Abnormal processing of sensory input by PNS or CNS
Centrally generated	• Deafferentation pain: injury to PNS or CNS (eg, phantom pain) • Sympathetically maintained pain: dysregulation of autonomic nervous system (eg, complex regional pain syndrome I and II)
Peripherally generated	• Painful polyneuropathies: pain is felt along the distribution of many peripheral nerves (eg, diabetic neuropathy) • Painful mononeuropathies: associated with a known peripheral nerve injury (eg, nerve root compression, trigeminal neuralgia)

Abbreviations: CNS, central nervous system; PNS, peripheral nervous system.

Data from Pasero C, McCaffery M. Pain assessment and pharmacologic management. (MO): Elsevier/Mosby; 2011.

Table 2
Nonopioid medications to reduce postoperative pain

Drug	Comment
Acetaminophen (paracetamol)	• Effective analgesic for acute pain • Incidence of adverse effects comparable with placebo • Reduces opioid consumption • Available IV
Nonselective NSAIDs (eg, ibuprofen, ketorolac, naproxen)	• Effective in treatment of acute postoperative pain • Reduces opioid consumption and incidence of nausea, vomiting, and sedation • Incidence of perioperative renal impairment is low[a] • Risk of gastropathy increased when ketorolac use exceeds 5 d • Patients should be well hydrated and without significant kidney disease • Ketorolac and ibuprofen available IV
COX-2 inhibitors	• Effective in treatment of acute postoperative pain • Reduce opioid consumption, and increase patient satisfaction • Do not result in a decrease in opioid-related side effects • Do not impair platelet function
Aspirin	• Increases bleeding after tonsillectomy
Ketamine: subanesthetic doses	• Acts primarily as noncompetitive antagonist of NMDA receptor • Effective adjuvant for pain associated with central sensitization (eg, severe acute pain, neuropathic pain, opioid-resistant pain) • May reduce CPSP and opioid-induced tolerance/ hyperalgesia • Opioid sparing; reduces incidence of nausea and vomiting • Safe and effective analgesic for painful procedures in pediatrics
Antidepressants and selective serotonin reuptake inhibitors	• Useful for acute neuropathic pain
Anticonvulsants (Gabapentin and pregabalin)	• Reduce postoperative pain, opioid requirements, and incidence of vomiting, pruritus, and urinary retention, but increase risk of sedation • May be useful for acute neuropathic pain (based on experience with chronic neuropathic pain)
IV lidocaine infusion	• Opioid sparing; reduced pain scores, nausea, vomiting and duration of ileus up to 72 h after abdominal surgery • May be useful agent to treat acute neuropathic pain
α_2 Agonists (clonidine, dexmedetomidine)	• Improves perioperative opioid analgesia. Decreased opioid requirements and opioid side effects • Side effects: sedation, hypotension

Abbreviations: COX-2, cyclooxygenase 2; IV, intravenous; NMDA, *N*-methyl-D-aspartate receptor; NSAIDs, nonsteroidal antiinflammatory drugs.

[a] Risk of adverse renal effects of nonselective NSAIDs and COX-2 inhibitors is increased in the presence of preexisting renal impairment, hypovolemia, hypotension, use of other nephrotoxic agents, and angiotensin-converting enzyme inhibitors.

Adapted from Macintyre PE, Schug SA, Scott DA, et al. APM: SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (2010), Acute Pain Management: Scientific Evidence (3rd edition), ANZCA & FPM, Melbourne; and Solomon DH. NSAIDs: therapeutic use and variability of response in adults. In: Furst DE, editor. UpToDate. Waltham (MA): UpToDate; 2014.

PREOPERATIVE MANAGEMENT

Preprocedure Evaluation

The management of surgical pain begins with the preprocedure evaluation. The anesthesia and surgical team should work closely before, during, and after the surgical procedure to optimize the patient's entire perioperative experience.[2]

The goal of the preoperative examination is to identify patients at risk for complications, along with any comorbidities that can be optimized. This is a good time to evaluate and determine information about previous and ongoing pain issues, as well as pain control methods that have worked or have failed to work in the past. It is also a time to assess for risk factors for postoperative pain.[10] A baseline pain assessment is an important part of any preoperative evaluation; however, standardization of the pain measurement can be difficult because of the subjective nature of the assessment. Because pain is a subjective experience modulated by factors such as previous events, culture, prognosis, coping strategies, fear, and anxiety, most measures of pain are based on self-report.[10]

Self-report measures are influenced by mood, sleep disturbance, and drugs. Postoperatively, it may not be possible to obtain reliable self-reports, because of impaired consciousness, cognitive dysfunction, extremes of age, and language barriers.[10] Some patients may be unable to understand a pain scale or may be unwilling to cooperate (eg, severe anxiety).[10] Pain scales presently used fall into multiple categories: single-dimension scales (visual analog and numerical rating scales) and multidimensional scales (McGill Pain Questionnaire).[10] It is important to assess not only a level of pain but the specific location of the pain and its character, duration, intensity, and frequency.

Patient Education

Patients are often concerned about their perioperative pain control, and the preoperative evaluation is an important opportunity to discuss the plan. A large part of patient education is setting the correct expectations of pain control in the perioperative period. The expectation should never be that the patient will have no pain.[2] Cognitive and psychological factors play a significant role in the severity of reported postsurgical pain, and evidence shows that psychological factors such as anxiety, depression, neuroticism, and catastrophizing are key determinants in the experience of pain (see **Table 1**).[1,6] The standard approach to provider education on pain emphasizes processes at the subcellular and cellular scale, with little attention given to the social component of pain, such as suffering, isolation, and pain behavior. Many physicians are therefore poorly prepared to deal with the social and psychological issues involved in treating postoperative pain in everyday clinical practice. Studies affirm that a dysphoric social dimension, isolation, withdrawal, distress, and the stigma of chronic pain contribute to the patient's multidimensional experience of pain almost as much as the physical nociception.[11] Failure to address this social dimension of pain can often render most standard pain management practices futile.

Preemptive and Preventative Analgesia Plan

Preemptive analgesia occurs when preoperative treatment is more effective than the identical treatment administered after incision or surgery. The only difference is the timing of administration. Preventative analgesia occurs when the intervention exceeds the expected duration of action of the intervention. The intervention may or may not be initiated before surgery.

The efficacy of preemptive analgesic interventions, such as epidural analgesia, local anesthetic wound infiltration, and use of nonsteroidal antiinflammatory drugs (NSAIDs), has been shown in a variety of settings.[1] Preventative analgesic interventions such as *N*-methyl-D-aspartate receptor antagonist drugs (ketamine and dextromethorphan) (see **Table 2**) and epidural analgesia have also been shown to have a salutary effect on postoperative pain.[1]

Choice of analgesia is highly dependent on the specific surgical procedure being performed, in terms of analgesic efficacy, potential side effects, and effects on recovery. The Prospect Working Group, composed of surgeons and anesthesiologists, has developed recommendations for pain management for a variety of adult elective surgeries, such as hemorrhoidectomy, inguinal hernia repair, laparoscopic cholecystectomy, noncosmetic breast cancer surgery, radical prostatectomy, open thoracotomy, primary total hip arthroplasty, and total knee arthroplasty. The recommendations follow a detailed methodology and are formulated based on evidence, with expert interpretation in the context of clinical practice. The evidence and recommendations for specific analgesia plans are freely accessible on the Internet.[3]

INTRAOPERATIVE MANAGEMENT

The surgical stress response is characterized by neuroendocrine, metabolic, and inflammatory changes, which can adversely affect organ function and perioperative outcomes and result in increased postoperative pain.[2] These responses are increased with the degree of surgical stimulation and magnified by hypothermia and psychological stress. Intraoperative surgical stress can be ameliorated with deeper planes of anesthesia, neural blockade, and reduction in the degree of surgical invasiveness, resulting in decreased postoperative pain. Specific methods used to decrease intraoperative stress include intravenous (IV) lidocaine, β-blockers, α_2 agonists, and regional anesthesia using local anesthetics.

Intravenous Medications

IV lidocaine with a bolus of 100 mg followed by an infusion of 2 to 3 mg/h has analgesic, antihyperalgesic, and antiinflammatory properties.[2] For colorectal and radical retropubic prostate surgeries, IV lidocaine has been shown to decrease the opioid requirements and facilitate early return of bowel function.[2]

β-Blockers have been used to blunt the sympathetic response to tracheal intubation and attenuate the surgical stress response of surgery. They reduce the requirement for volatile anesthetic agents and also have an opioid sparing effect.[2]

The α_2 agonists clonidine and dexmedetomidine have anesthetic and analgesic properties, which decrease postoperative pain and reduce opioid consumption and opioid-related side effects.[2] Dexmedetomidine is more selective than clonidine for the α_2 effects, with a half-life of about 2 hours. Unlike clonidine, dexmedetomidine can be given IV. Dexmedetomidine causes hyperpolarization of locus ceruleus neurons, which results in decreased activity in ascending noradrenergic pathway, inhibition of sympathetic-mediated pain at peripheral nociceptors, inhibition of substance P and glutamate release at primary afferent neurons, and inhibition of firing at second-order neurons.[12] Side effects include sedation and hypotension. The use of α_2 agonists consistently improves opioid analgesia, but the side effects may limit their clinical usefulness.[1] Dexmedetomidine should not be used in patients with advanced heart block, severe ventricular dysfunction, and shock, and clearance is lower in patients with hepatic impairment. Dexmedetomidine is used only

in a monitored setting (eg, operating room, intensive care unit [ICU]). Unlike opioids, dexmedetomidine is associated with minimal to no respiratory depression.

Neuraxial Techniques

Neuraxial blockade of nociceptive stimuli by an epidural or spinal anesthetic can blunt the metabolic and neuroendocrine stress response to surgery.[2] The epidural blockade should be provided with a solution of local anesthetic and low-dose opioid and established before surgical incision and continued postoperatively. Neuraxial techniques not only provide excellent analgesia but can also facilitate mobilization and physical therapy postoperatively.[13] They have also been associated with a decreased incidence and severity of ileus.[2] A thoracic epidural is recommended for surgeries including but not limited to open colorectal, thoracic, esophageal, aortic, and renal surgery. A lumbar epidural is usually not recommended for most abdominal surgery, because of questionable adequate segmental analgesia, high degree of urinary retention, and lower limb motor and sensory blockade, all of which delay mobilization.[2]

Contraindications to neuraxial anesthesia include patient refusal, bleeding diathesis, severe hypovolemia, increased intracranial pressure, and infection at the site of injection. Relative contraindications include severe aortic or mitral stenosis, severe left ventricular outflow obstruction, the presence of sepsis or bacteremia, and patients with dementia, psychosis, or emotional instability, which may make catheter placement more difficult.[2] Complications of neuraxial blockade include inadequate analgesia, intravascular injection, total spinal anesthesia, subdural injection, backache, postdural puncture headache, neurologic injury, epidural hematoma, meningitis, epidural abscess, and shearing of the catheter.[2]

Transversus Abdominus Plane Blocks

The transversus abdominus plane (TAP) block is a peripheral nerve block that anesthetizes the abdominal wall and can be an effective adjunct to multimodal postoperative analgesia after abdominal surgical procedures.[14] The TAP block is most often used to provide surgical anesthesia for minor, superficial procedures of the lower abdominal wall and postoperative pain control for procedures below the umbilicus.[2] The use of this block may decrease need for opioid therapy, thereby reducing the incidence of respiratory depression.[15] Main disadvantages of the TAP block are the limited duration of action with a single shot of local anesthetic and the sparing of the upper thoracic dermatomes.[15]

Peripheral Nerve Blocks

Continuous peripheral nerve blocks affect the afferent nociceptive pathways and are an excellent way to decrease the required doses of opioids.[2,16] Specific types of peripheral blocks are noted in **Tables 3–5**. Contraindications and risks of peripheral nerve blockade include inability of the patient to cooperate, bleeding disorders, pharmacologic anticoagulation, infection at the site, preexisting nerve damage, and allergy to local anesthetics.[2]

Wound Infiltration Anesthesia

Local anesthesia may be accomplished by infiltration of the wound with lidocaine or bupivacaine.[17] Onset of action is rapid after intradermal or subcutaneous administration and epinephrine prolongs the duration of anesthesia.[18] The dose of local anesthetic required depends on the extent of the area to be anesthetized and the expected duration of the surgical procedure. In patients undergoing colorectal

Table 3
Upper extremity blocks

Type	Nerves Blocked	Indication/Procedure Site	Contraindication
Interscalene brachial plexus	C5–7	• Shoulder and upper arm	• Severe pulmonary disease • Preexisting contralateral phrenic nerve palsy
Supraclavicular	Brachial plexus	• At or below the elbow • Ideal for catheter placement	• Severe pulmonary disease • Preexisting contralateral phrenic nerve palsy
Infraclavicular	Brachial plexus	• Distal to the elbow	• Vascular catheters in this region • Ipsilateral pacemaker
Axillary	Brachial plexus	• Distal to the elbow	

Data from Butterworth J, Mackey D, Wasnick J. Morgan and Mikhail's clinical anesthesiology. New York (NY): Lange/McGraw-Hill; 2013.

surgery, local anesthetic wound infiltration techniques reduced opioid requirements and pain scores and improved recovery compared with placebo/routine analgesia.[19] However, diverse study design is a major limitation of this analysis. Liposomal bupivacaine (Exparel) has been developed to allow for a prolonged duration of effect, because significant bupivacaine plasma concentrations can remain up to 96 hours after single-dose administration. A pooled analysis of several studies evaluating the effect of liposomal bupivacaine[20] showed decreased postoperative pain after 72 hours

Table 4
Lower extremity blocks

Type	Nerves Blocked	Indication/Procedure Site	Contraindication
Lumbar plexus	L1–4	• Anterior thigh and medial leg	
Sacral plexus	L4–5 and S1–4	• Posterior thigh and most of leg and foot	
Femoral		• Hip, thigh, knee, and saphenous nerve of the ankle	• Previous vascular grafting • Local adenopathy
Lateral femoral cutaneous	L2–3	• Lateral thigh	
Obturator		• Complete anesthesia of the knee	
Saphenous	Most medial branch of the femoral nerve	• Medial leg and ankle	
Sciatic	L4–5 and S1–3	• Hip, thigh, knee, lower leg and foot	
Ankle	1. Saphenous nerve 2. Deep peroneal 3. Superficial peroneal 4. Posterior tibial 5. Sural	• Foot	

Data from Butterworth J, Mackey D, Wasnick J. Morgan and Mikhail's clinical anesthesiology. New York (NY): Lange/McGraw-Hill; 2013.

Table 5
Blocks of the trunk

Type	Nerves Blocked	Indication	Risks
Superficial cervical plexus	C1–4	• Cutaneous analgesia to the neck, anterior shoulder, and clavicle	
Intercostal	Individual injection at the vertebral level required	• Analgesia after thoracic and upper abdominal surgery • Rib fracture • Herpes zoster • Cancer	• Highest complication risk of any block • Results in highest blood levels of local anesthetic per volume injected of any block • Pneumothorax
Paravertebral	Individual injection at the vertebral level required	• Procedures of the thoracic and abdominal wall • Mastectomy • Inguinal or abdominal hernia • Nephrectomy	• Sympathectomy • Pneumothorax

Data from Butterworth J, Mackey D, Wasnick J. Morgan and Mikhail's clinical anesthesiology. New York (NY): Lange/McGraw-Hill; 2013.

and a decrease in opioid consumption when compared with nonliposomal bupivacaine. There are still only a few comparative studies using liposomal bupivacaine, and its use may be limited by the significant difference in cost compared with bupivacaine hydrochloride. Dosing and duration of action for selected local anesthetics are shown in **Table 6**.

Tumescent Anesthesia

Tumescent anesthesia refers to subcutaneous injection of large volumes of dilute local anesthetic in combination with epinephrine and other agents.[18] The doses of lidocaine range from 35 to 55 mg/kg and are associated with plasma concentrations that may peak at more than 8 to 12 hours after the procedure. This technique of local anesthesia is most frequently used by plastic surgeons during liposuction surgery. Although generally safe with proper use, cases of high local anesthetic concentrations and cardiac arrest and death have been reported with this technique.

Topical Local Anesthesia

Local anesthetic formulations have been developed to penetrate intact skin. EMLA is a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine base. It can be used for

Table 6
Local anesthetic dosing for infiltration anesthesia

Drug	Maximum Dose* (mg) Plain	Duration (min) Plain	Maximum Dose* (mg) with Epinephrine	Duration (min) with Epinephrine
Lidocaine	300	30–60	500	120
Bupivacaine	175	120–240	200	180–240

* For an average 70 kg adult.
Data from Gandhi G, Baratta JL, Heitz JW, et al. Acute pain management in the postanesthesia care unit. Anesthesiol Clin 2012;30(3):1–15.

venipuncture, IV cannulation, skin grafting, and circumcision. EMLA is applied under an occlusive bandage for 45 to 60 minutes to obtain effective cutaneous anesthesia. There is a risk of methemoglobinemia from prilocaine.[18]

Topical anesthesia can also be applied through cut skin to facilitate suturing of lacerations in pediatrics (eg, lidocaine-epinephrine-tetracaine and tetracaine-phenylephrine) and for mucosal analgesia and vasoconstriction (eg, oxymetazoline or phenylephrine and lidocaine).

POSTOPERATIVE MANAGEMENT

Opioids

Opioids remain the cornerstone of the management of surgical pain, despite their potential side effects (**Table 7**), and can be given through IV, intramuscular, oral, or transdermal routes. IV opioids provide rapid and effective analgesia for patients with moderate to severe pain. Morphine is the prototypical opioid agonist and the standard for management of acute pain. It has moderate analgesic potency, slow onset, and intermediate duration of action. The half-life is 2 hours, and its duration of action is about 5 hours. The metabolites of morphine are excreted by the kidney, and, therefore, the sedating effects can be prolonged in patients with renal failure.[21]

Hydromorphone is a semisynthetic opioid, which is 4 to 6 times more potent than morphine. The onset of action is more rapid than morphine, but the duration of action is shorter. It is a better choice for patients with renal failure and has a lower incidence of pruritus and sedation than morphine. It is particularly useful in patients who are opioid tolerant.[21]

Fentanyl is a synthetic opioid, which is 50 to 80 times more potent than morphine. It has a rapid onset of within 5-7 minutes, with a short duration of only about 1 hour. IV

Table 7
Adverse effects of opioids

Adverse Effect	Comment
Respiratory depression	• Dose related. Decreased central CO_2 responsiveness → hypoventilation, increased arterial CO_2 levels, decreased respiratory rate, and oxygen saturation • Best early clinical indicator is increasing sedation
Nausea and vomiting	• Dose related • Significantly reduced by droperidol, dexamethasone, and ondansetron
Impaired gastrointestinal motility	• Opioids impair return of bowel function after surgery • May be reversed by peripheral acting opioid antagonists
Urinary retention	• Reversed by naloxone
Pruritus	• Can be effectively treated with naloxone, naltrexone, nalbuphine, and droperidol
Delirium and cognitive dysfunction	• Increased risk of delirium with meperidine
Tolerance and hyperalgesia	• Tolerance = desensitization of antinociceptive pathways to opioids • Opioid-induced hyperalgesia = sensitization of pronociceptive pathways → pain hypersensitivity

Data from Macintyre PE, Schug SA, Scott DA, et al. APM:SE Working Group of the Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (2010), Acute Pain Management: Scientific Evidence (3rd edition), ANZCA & FPM, Melbourne.

fentanyl can be particularly effective when rapid analgesia is needed, such as in the postanesthesia care unit or ICU. Transdermal fentanyl is an alternative to sustained-release oral morphine and oxycodone preparations. These patches have a drug reservoir, which is separated from the skin by a microporous rate-limiting membrane, and provide medication that last for 2 to 3 days.[2] Fentanyl absorption lasts for several hours, even once the patch is removed. Disadvantages of the transdermal route include the slow rate of onset and the inability to rapidly change dosage, as blood levels of fentanyl increase and plateau at 12 to 40 hours. Safety alerts have been issued warning against use of fentanyl patches in opioid-naive patients, and potentially dangerous increases in serum fentanyl levels occur with increased body temperature or exposure of patches to external heat sources.[2,22]

Meperidine lowers seizure threshold, has a dysphoric effect, and is not recommended for postoperative pain control. In addition, meperidine has a slower rate of metabolism in the elderly and in patients with hepatic and renal impairment, leading to accumulation of meperidine and its active metabolite normeperidine, and consequent risk for seizures.[1]

Oxycodone is a potent opioid agonist, which is metabolized in the liver. In an experimental pain model, oxycodone was more effective than morphine for pain related to mechanical and thermal stimulation of the esophagus, suggesting that it could be more effective than morphine for visceral pain.[1]

Tramadol is an effective analgesic for mild to moderate pain and neuropathic pain. The risk of respiratory depression is less compared with other opioids, and significant respiratory depression has been reported only in patients with severe renal failure.[1]

Patient-Controlled Analgesia

Patient-controlled analgesia (PCA) provides better pain control, greater patient satisfaction, and fewer opioid side effects when compared with on-request opioids.[21] The PCA is based on the idea of a negative feedback loop.[23] When the patients experience pain, they self-administer medication, and once the pain is reduced, they stop giving themselves medication.[23] Patients should be given a loading dose of opioid until a reported pain score of 4 out of 10 is achieved or a respiratory rate of fewer than 12 breaths per minute, before the PCA is begun.[21] The PCA is then programmed as a bolus dose, which the patients receive each time they press the button. The maximum number of doses is limited per hour. There is also a lockout interval of time, which limits how closely consecutive doses can be given. The PCA is usually used with morphine or hydromorphone. Fentanyl PCA is often restricted to hospital units with continuous monitoring, such as the ICU, secondary to the increased risk of respiratory depression. Sufentanil is another potent opioid that can be used for PCA. Sublingual sufentanil 15 μg microtablets (sufentanil nanotab PCA system; AcelRx Pharmaceuticals, Inc., Redwood City, CA) has recently been shown to provide an alternative to IV PCA for adult inpatients after major open abdominal or orthopedic surgery.[24] However, the nanotab oral/transmucosal delivery system is not approved for clinical use.

NONOPIOID ANALGESICS

Nonsteroidal Antiinflammatory Drugs

NSAIDs such as ibuprofen, ketorolac, naproxen, and cyclooxygenase 2 (COX-2) inhibitors are effective analgesics in a variety of acute pain states and have a broad spectrum of antiinflammatory and antipyretic effects (see **Table 2**).[1] IV ketorolac is widely used during the perioperative period for short-term treatment of acute pain and as an adjunct to opioids for the treatment of moderate to severe postoperative pain. Maximal benefit

occurs when the NSAID is continued for 3 to 5 days postoperatively.[25] The addition of NSAIDs to systemic opioids diminishes postoperative pain intensity, reduces opioid requirements, and decreases opioid side effects, such as postoperative nausea and vomiting and respiratory depression.[2] NSAIDs are the key components of multimodal analgesia but are generally inadequate as the sole analgesic agent in control of severe postoperative pain. When used in combination with opioids, NSAIDs improve analgesia, decrease opioid consumption, and decrease incidence of opioid-related adverse effects, such as postoperative nausea, vomiting, and sedation.[1]

NSAIDs increase the risk of gastrointestinal bleeding and postoperative bleeding, decreased kidney function, impaired wound healing, and risk of anastomotic leakage.[2] Their use should therefore be guided by the type of surgery being performed and by consultation between the surgical and anesthesia teams. COX-2 inhibitors also reduce postoperative pain, with less risk of NSAID-related platelet dysfunction and bleeding, but are associated with cardiovascular risk in the perioperative period.[2] The risk of adverse renal effects of nonselective NSAIDs and COX-2 inhibitors is increased in the presence of preexisting renal impairment, hypovolemia, hypotension, and use of other nephrotoxic agents and angiotensin-converting enzyme inhibitors.

Acetaminophen

Oral, rectal, and parenteral acetaminophen (paracetamol) can be an effective component of multimodal anesthesia. Acetaminophen significantly reduces pain intensity and spares opioid consumption after abdominal surgery. The analgesic effect is 30% less than that of NSAIDs, but side effects are fewer.[2] Acetaminophen can also be used in conjunction with an NSAID to improve postoperative analgesia and as an adjunct to PCA opioids to reduce morphine requirements.[26,27] The primary concern with use of acetaminophen is hepatotoxicity, which is most concerning in the elderly and patients who chronically consume alcohol.[22]

Antidepressants

Antidepressants are useful for patients with neuropathic pain, even when depression is not a diagnosis of the patient. The analgesic effects occur at lower doses than needed for antidepressant activity. Older tricyclic agents, such as amitriptyline and nortriptyline, which block the reuptake of serotonin and norepinephrine, seem to be more effective than selective serotonin reuptake inhibitors.[2] The onset of pain relief is usually not immediate and may take weeks to have a complete effect. Antidepressants work best for pain from nerve damage secondary to diabetes, peripheral neuropathy, spinal cord injury, stroke, and radiculopathy.[2]

Anticonvulsants

Anticonvulsant medications are useful for patients with neuropathic pain as well as for suppressing postoperative pain.[28] The most commonly used agents include gabapentin, phenytoin, carbamazepine, and clonazepam. Pregabalin is a newer agent, which has been approved for all forms of neuropathic pain.[2] The synergism between gabapentin and opioids results in an opioid sparing effect.[28] Procedures in which gabapentin use for postoperative pain relief has been studied include breast surgery, hysterectomy, spinal surgery, postamputation, orthopedic surgery, and postthoracotomy.[28]

Corticosteroids

Corticosteroids when used as an adjuvant decrease opioid consumption and help reduce postoperative pain.[25] Dexamethasone is the preferred corticosteroid, because it also reduces postoperative nausea and vomiting.

Ketamine

Ketamine can be used as an antihyperalgesic in the perioperative period.[7] Although traditionally used intraoperatively, low-dose ketamine has increasingly been given for postoperative analgesia.[23] Perioperative subanesthetic doses have been shown to decrease the opioid requirements and decrease the reported pain intensity.[23] At the low doses used in the postoperative period, ketamine does not result in the hallucinations or cognitive impairment that are often seen with high doses.[23]

Local Anesthetics

The lidocaine patch is primarily used for relief of allodynia (painful hypersensitivity) and chronic pain in postherpetic neuralgia. Onset is approximately 4 hours. Absorption is dependent on dose, application site, and duration of exposure. The time to peak effect of 5% transdermal lidocaine is approximately 11 hours after application of 3 patches. Lidocaine patches have been used successfully for the treatment of pain secondary to rib fractures, back pain, and orthopedic surgeries. On-Q is a system that uses a catheter temporarily implanted in an incision, allowing for continuous release and infiltration of local anesthetic agents. Studies have suggested clinical benefit with use of this system after abdominal, gynecologic, and thoracic surgeries.[1,29,30] A meta-analysis of studies using the system after colorectal surgery via laparotomy[31] showed a reduction in pain with movement and decrease in total opioid consumption, but no decrease in length of stay or ileus. Definitive conclusions about the overall benefit of this approach await further study.

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) produces analgesia by stimulating large afferent fibers.[2] Although not commonly used, TENS has been shown to decrease postoperative pain, with little if any risk to the patient, and can be used to treat mild to moderate acute pain.[2,25]

MULTIMODAL

The best treatment plan for a patient's postsurgical pain is the multimodal approach. By using a combination of the medications and techniques discussed in this article, the physician is able to create a personalized treatment plan that takes into account the patient's personal and medical needs. Multimodal pain management combines the use of different pharmacologic mechanisms of action and additive or synergistic effects, which work by acting at different sites within the central and peripheral nervous system.[25] The goal is to provide optimal pain control, limit the amount of opioids required after surgery, and therefore, decrease their associated adverse effects.

Once the multimodal plan is established, the patient must be followed to determine whether the plan is meeting the patient's needs or if any changes need to be made. This follow-up includes routine monitoring of vital signs and oxygenation. The nursing staff should closely monitor for and report any side effects (**Table 8**). However, successful management of acute postoperative pain requires close liaison with all personnel involved in the care of the patient. Many institutions now have an acute pain service (APS), which can be called on to deal with complex pain management issues such as acute on chronic pain, acute pain after major trauma, opioid-tolerant patients, and specific patient populations. There is daily clinical participation of anesthesiologists, together with input from other physicians and staff, leading to

Table 8
Monitoring for potential side effects of postoperative analgesia

System	Side Effect
Cardiovascular	• Hypertension/hypotension • Bradycardia/tachycardia
Respiratory	• Hypoventilation • Hypoxia
Gastrointestinal	• Nausea • Vomiting • Ileus
Urinary	• Urinary retention
Neurologic	• Change in mental status • Sensory or motor block
Hematologic	• Hematoma at neuraxial catheter/peripheral nerve catheter site (impaired neurologic function as well)
Skin	• Rash • Pruritus

maximum patient benefit. Implementation of an APS may improve pain relief and reduce the incidence of side effects.

SPECIAL CONSIDERATIONS

Ambulatory Surgery

The number of outpatient surgical procedures continues to increase. With this increase, the complexity of the procedure and patient comorbidity are also increasing. Inadequate pain control is one of the leading causes of prolonged stays and readmission after outpatient surgery.[23] Despite advances in surgical technique, the incidence of moderate to severe postoperative pain on discharge is still about 25% to 35%.[25]

The traditional reliance on opioid-based pain management may not be ideal in the ambulatory setting, because many of the side effects may delay discharge. Using nonopioid techniques with different mechanisms of action, such as acetaminophen, NSAIDs, local anesthetics, nerve blocks, tissue infiltration, wound instillation, or topical anesthetics, may give improved pain management, with fewer side effects.

Pediatrics

Undertreatment of acute pain is common with children.[23] In addition to anatomic, physiologic, pharmacodynamic, and pharmacokinetic differences, there are unique barriers to the treatment of postoperative pain in children. One of the myths is that children and infants do not feel pain or that the pain is not remembered, and therefore, there is no consequence of experiencing the pain. This theory is false, and poor pain control has been associated with increased morbidity and mortality.[23] Pediatric patients often have difficulty communicating their pain, and special scales are available to assist in self-reporting.

Children as young as 4 years old have been reported to have the cognitive and physical ability to use an IV PCA device.[23] For the child who is unable to use PCA, intermittent boluses are recommended. With the exception of the child with sleep apnea, respiratory depression after opioids is rare in children, compared with adults. The use of NSAIDs or acetaminophen may improve the overall analgesia and reduce the

opioid use. Peripheral and neuraxial techniques can be used in the pediatric population as well.[23]

The Elderly

The elderly population will continue to increase in the next several decades. The elderly have changes in their physiology, pharmacokinetics, pharmacodynamics, and nociceptive processing, which influence the effectiveness of the standard pain management techniques. In addition, the elderly may present with other barriers, such as communication, social, and cognitive issues, which may limit effective postoperative pain control. The elderly are at increased risk of postoperative complications, especially in the presence of severe or uncontrolled pain.[23]

As a patient ages, there are reported decreases in the intensity of pain perception and symptoms. This change was documented in studies of myocardial infarctions lacking in angina symptoms. Studies have shown a decrease in Aδ and C fiber nociceptive function, delay in central sensitization, increase in pain thresholds, and decreased sensitivity to low-intensity noxious stimuli.[23] However, these studies have also shown that the elderly had an increased response to high-intensity stimuli, decreased pain tolerance, and decreased descending modulation, which may explain the high incidence of elderly patients reporting chronic postoperative pain.[23] Physiologic changes in the elderly patient include longer circulation times and longer duration of action secondary to reduced clearance of medications, and analgesic requirements tend to decrease with increasing age.[23] IV PCA is appropriate in the elderly, because it allows the patient to compensate for individual variability. Use of patient-controlled epidural analgesia has been reported to improve postoperative outcomes, such as gastrointestinal function after abdominal surgery, decreased incidence of myocardial infarction, decreased pain scores, and decreased pulmonary complications.[23]

Delirium is one of the most significant complications in elderly patients after surgery and is associated with increased mortality and prolonged hospital stays. Delirium is multifactorial, but uncontrolled pain may be a contributor to its development, because higher pain scores have been associated with a decline in mental status and development of postoperative delirium.[23] Opioids other than meperidine have not been associated with the development of delirium.

Obesity and Obstructive Sleep Apnea

Patients with obstructive sleep apnea (OSA) may be at a higher risk for postoperative complications. During obstructive episodes, patients with OSA may show hypoxia, bradyarrhythmias or tachyarrhythmias, myocardial ischemia, and decreased cardiac output.[23] Postoperative pain management is therefore more complicated in the patient with OSA. Patients with OSA are at an increased risk for respiratory arrest, and the use of sedatives, such as benzodiazepines and opioids, may be especially dangerous. Avoiding respiratory depressants and optimizing the use of NSAIDs and epidural analgesia with a local anesthetic instead of opioids may attenuate the risk for respiratory depression and arrest.

Patients with diagnosed OSA who require postoperative opioid therapy should be admitted to the hospital overnight and continuously monitored by pulse oximetry.[23] This strategy is especially true of high-risk children after tonsillectomy and adenoidectomy, because the surgery involves the airway and the patients receive opioids for pain.[32] Moreover, children with sleep-disordered breathing and recurrent hypoxemia are more sensitive to the effects of opioids and require dose reductions.[33] Codeine is best avoided, because some children have increased conversion of codeine to

morphine (extensive and ultrarapid metabolizer phenotypes), which can lead to an overdose.[34]

Acute on Chronic Pain

Patients with chronic pain conditions need to have a specific plan for the management of their postoperative pain, particularly patients already taking large doses of analgesics or patients with a history of analgesic abuse.[10] Postoperative pain management may be difficult in opioid-tolerant patients, because the standard assessment and therapy approaches are usually inadequate. Opioid-tolerant patients usually require higher doses of analgesic medications, but health care providers are often afraid to prescribe them as needed, because of concern for addiction or medication-related side effects and mistaking tolerance for addiction.[10] An APS, if available, should be consulted before surgery, and the patient's personal chronic pain physician should be contacted for perioperative recommendations. It is important to develop a treatment plan before surgery, and this plan should be discussed with the patient and the perioperative management teams. It is also important to recognize and address nonnociceptive sources of distress.[10] Patients on chronic pain medications should not have the medications weaned or held before surgery, unless they are using an NSAID or COX-2 inhibitor that needs to be held preoperatively. Patients should be told to take their usual morning does of pain medication, and all transdermal patches should remain on during the surgery. Even if they are already on high doses of pain medications, the chronic pain patient's postoperative analgesic needs should be expected to increase.[10]

High self-reported pain scores should also be expected, and therefore, treatment should be based on other assessments, such as ability to breathe deeply, cough, and ambulate, in conjunction with the patient's self-reported pain scores. The patient's required maintenance medications should continue, with additional medications added to treat the new surgical pain. Adjuvants such as NSAIDs and regional anesthesia techniques as well as a plan to transition the patient from IV to oral medications are all necessary. The oral medications should include a scheduled long-lasting controlled-release opioid as well as an as-needed immediate-release opioid for breakthrough pain. It is also important for the physician to recognize that the perioperative period is not the appropriate time to detoxify the patient.[23]

SUMMARY

Postoperative pain is an individual multifactorial experience influenced by patient culture, psychology, genetics, previous pain events, beliefs, mood, and ability to cope, as well as the type of procedure performed. Inadequate treatment of postoperative pain continues to occur, despite advances in analgesic techniques, placing patients at risk for CPSP and significant disability. Optimal pain results from proper management in the preoperative, intraoperative, and postoperative periods and requires appropriate education of physicians, nurses, other health care providers, and patients. An understanding of the pathophysiology of postoperative pain and the various options available for analgesia often results in a procedure-specific, multimodal approach, optimizing pain relief, decreasing adverse effects, and creating a better patient experience.

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