Postoperative Pain Management

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ABSTRACT

After surgery, over 80% of people experience moderate-to-severe acute pain. Poorly controlled postoperative pain limits recovery and is associated with detrimental short- and long-term morbidity. While surgeons have traditionally been responsible for postoperative pain management, all clinicians providing care for surgical patients have a basic understanding of common pharmacologic and interventional pain management strategies. In this review, we discuss the consequences of acute pain, approaches to pain assessment, and an overview of commonly used therapies to manage postoperative pain.

RÉSUMÉ

Après une opération, plus de 80 % des gens ressentent des douleurs aiguës modérées à intenses. Une douleur postopératoire mal maîtrisée limite le rétablissement et est associée à une morbidité défavorable à court et à long terme. Bien que les chirurgiens soient habituellement responsables du traitement de la douleur postopératoire, il est impératif que tous les cliniciens qui soignent des patients ayant subi une intervention chirurgicale aient une connaissance de base des stratégies pharmacologiques et interventionnelles courantes relatives au traitement de la douleur. Dans cette revue, nous abordons les conséquences de la douleur aiguë, les approches de l'évaluation de la douleur et un aperçu des traitements couramment utilisés pour traiter la douleur postopératoire.

Key Points

- Acute pain is common after surgery and many patients will suffer from moderate-to-severe postoperative pain.
- Postoperative pain is associated with poor clinical outcomes, patient dissatisfaction, and long-term morbidities such as chronic post-surgical pain.
- Comprehensive pain assessments are needed to plan for the use of analgesic therapies preoperatively, intraoperatively, and postoperatively.
- Multimodal analgesia is the optimal treatment strategy and includes the use of several different therapies to achieve adequate pain control.

Introduction

Postoperative pain is one of the most significant concerns for patients when undergoing surgery¹ and is a strong predictor of whether patients are satisfied with their perioperative care.² Unfortunately, approximately 88% of patients report moderate-to-severe acute pain after surgery.³ Unmanaged postoperative pain has consequences which include deleterious physiological effects, increased healthcare utilization, and poor clinical outcomes, such as acute pain predisposing to the development of chronic post-surgical pain (CPSP).^{4,5} While our understanding and tools to manage pain have improved, inadequately controlled postoperative pain continues to be an unresolved global health-care problem. Furthermore, the recent and ongoing opioid epidemic has increased pressure to reduce opioids during and after surgery as a strategy to mitigate the rates of persistent opioid use.⁴ As such, there is increasing interest to provide multimodal analgesia and identify novel interventions to improve postoperative pain management and reduce persistent post-surgical opioid use.

While postoperative pain has traditionally been the primary responsibility of surgeons, successful management of postoperative pain requires a multidisciplinary approach that involves anesthesiologists, internists, perioperative physicians, and family physicians.⁶ An understanding of postoperative pain and commonly used interventions are required for effective management of patients undergoing surgery. This article aims to provide a basic overview of the principles, approaches, and strategies to manage acute postoperative pain.

Physiology of Acute Postoperative Pain

Postoperative pain refers to pain immediately after surgery and can persist for weeks and months. The International Association for the Study of Pain proposes that the normal healing time following surgery is approximately 3 months, and any pain after this period (that did not exist prior to surgery), should be considered pathologic (i.e., CPSP).⁷

Acute surgical pain is described as nociceptive pain that is well-localized and characterized as sharp, aching, or throbbing. It is triggered by the activation of local peripheral nociceptive fibers, specifically the lightly myelinated A-delta and slow-conducting unmyelinated C fibers.⁸ These fibers are activated via thermal, mechanical, and chemical-induced tissue injury.⁹ Surgery results in direct activation of these nociceptive fibers through mechanical trauma from a surgical incision, manual handling of tissues, and surgical retraction. As such, acute pain is influenced by the location of surgery, its extent, and degree of tissue and neuronal traumatization.¹⁰ These mechanical injuries initiate an inflammatory cascade of events that result in an outpouring of mediators including potassium, adenosine-triphosphate, sodium, nerve growth factor (NGF), tumor necrosis

factor-alpha (TNF- α), prostaglandins, bradykinins, histamines, and interleukins^{11,12} that result in further chemical-induced activation of local nociceptive fibers.

Nociceptive input from A-delta and C fibers enters the spinal cord via the dorsal horn and synapses with second-order neurons at A-delta at Laminae II and V, C and Laminae II. From here, pain signals cross to ascending spinothalamic and spinoreticular pathways to ultimately reach higher brain centers. Spinothalamic tract neurons synapse with third-order neurons in the thalamus, relaying the signal to the cortex, and spinoreticular tract neurons synapse in the brainstem with projections to the thalamus, hypothalamus, and cortex, and are involved in the emotional and psychological experience of pain. Given the multiple triggers involved in postoperative pain, effective pain management strategies aim to address specific nociceptive triggers (i.e., inflammation from the surgical incision, neuropathic pain from local nerve injury) and sites (e.g., dorsal horn where opioids act) along the pain pathways.

Clinical Consequences of Acute Pain

There are several physiological and clinical consequences of postoperative pain (Table 1).⁴ Pain contributes to increased heart rate, hypertension, increased myocardial contractility, and potentially myocardial ischemia.¹³ Pain also alters normal respiratory function via splinting of the abdominal muscle, diaphragmatic dysfunction, reduced vital capacity, and inability to cough, especially for surgeries that require an abdominal incision. Other physiological effects of postoperative pain include reduced intestinal motility, altered renal physiology, impaired immune and coagulation function, muscle weakness, sleep disruption, and psychological distress.¹³ Furthermore, from a healthcare resource perspective, acute postoperative pain also results in prolonged recovery room stay, delayed hospital discharge, and unanticipated admissions or readmissions after surgery.^{14–16}

Table 1. Consequences of Inadequate Postoperative Pain

Patient
<ul style="list-style-type: none"> • Reduce QoL • Impaired sleep • Impaired physical activities, which may delay recovery • Impaired mental status • Develop chronic pain
Hospital
<ul style="list-style-type: none"> • Increase postoperative readmission • Increase ED visit for refilling pain medications
Society
<ul style="list-style-type: none"> • Increase cost of care • Long-term opioid use

QoL = Quality of Life; ED = Emergency Department.

Poorly controlled acute pain after surgery has an impact on a patient's well-being long after the immediate postoperative period. Patients with moderate-to-severe pain (≥ 4 on a 0–10 scale) within 4 days after surgery were at increased risk of functional limitations, poor recovery, and decreased quality of life 6-months after surgery.¹⁷ Furthermore, greater acute pain is a predictor of the development of CPSP.¹⁸ CPSP has recently been designated as a separate pain disorder by the International Classification of Diseases,⁷ and is associated with reduced physical function, psychological and emotional distress, and poor quality of life.¹⁹

Assessment of Pain

An accurate assessment of pain is critical to effective pain management. Pain is a subjective experience and is influenced by the patient's genetics, emotions, mood, and other ongoing medical issues. It is important that the patient's pain is assessed using validated pain intensity instruments. Pain intensity scales are often used and include the Numeric Rating Scale (0 to 10 scale where 0 represents no pain and 10 represents worst imaginable pain), Verbal Rating Scale (comprises a list of adjectives used to denote increasing pain intensities), and the Visual Analog Scale (a 10-cm line anchored by verbal descriptors of "no pain" and "worst imaginable pain" and the patient is asked to mark a line to indicate pain intensity).⁶ There is insufficient evidence to recommend a specific pain assessment tool over another in the postoperative period, although the numerical rating scale (NRS) is the most commonly used, with satisfactory analgesia commonly occurring with ≤ 3 out of 10, and an estimated minimally important difference of 2 points.²⁰ Additionally, the Brief Pain Inventory (BPI) is a simple and easy tool for assessing pain and is useful in chronic or cancer pain; however, it is not clinically feasible to assess acute surgical pain due to pain dynamics and high frequency for assessments by nurses. Assessing pain in older adults or those with cognitive impairments presents greater challenges. Observation scales, such as the Abbey pain scale, use observed behavior and physiological parameters to give a numerical pain assessment.²¹

It is imperative that pain is not only evaluated at rest but also in movement. Movement-evoked pain is often neglected; however, it is estimated to be 95–226% more intense than pain at rest and more directly affects post-surgical functional recovery.²² A surrogate measure of pain intensity in the postoperative period is opioid consumption. If opioids are available on an "as needed" basis and patients have increased pain, their opioid usage will increase. Some have argued that a composite score of pain intensities and opioid consumption should be considered for a more valid assessment of pain.²³ Additional elements of a postoperative pain assessment should include the onset and pattern of pain, location, quality of pain, aggravating and

alleviating factors, previous effective or ineffective therapies, and effect of pain on sleep, mood, emotions, and physical function.²⁴

Overview of Acute Pain Management

Professional association guidelines (American Pain Society [APS], the American Society of Regional Anesthesia and Pain Medicine [ASRA], and the American Society of Anesthesiologists [ASA]) have provided general recommendations for optimal postoperative pain management.²⁴ These recommendations include preoperative education, accurate pain assessment, multimodal analgesia, and transitional management (Table 2). They particularly emphasize the importance of patient education and reducing opioids after surgery. Of note, positive and goal-directed patient expectation enhances early recovery from surgery, and postoperative opioid tapering should be planned by both hospital specialists and family physicians. Adequate pain management promotes patient recovery and rehabilitation and might reduce postoperative adverse events, even healthcare costs as well.²⁵ The goal of postoperative pain management should be not to eliminate pain (i.e., achieving zero pain). Aiming for complete pain relief may prove challenging and can lead to overuse of pain medications. Clinicians should aim to balance the efficacy and side-effects of pain therapies.

The optimal management of postoperative pain first begins preoperatively. Identifying those at high risk of acute postoperative pain allows for early consideration of preventative analgesics (i.e., preoperative and intraoperative medications or interventions) (Table 2). Preoperative pain, chronic opioid use, pain catastrophizing, and type of surgery, specifically orthopedics, urologic, general surgery, and plastic surgery, are all risk factors for increased postoperative pain.^{26–29} Further, younger age, females, preoperative pain, and opioid use, increased postoperative pain, and psychological factors (i.e., depression, anxiety, and catastrophizing), appear to be risk factors for CPSP.³⁰

Multimodal analgesia is the desired method for postoperative pain management. This includes combining different analgesic therapies to provide analgesia while minimizing the side-effect of each medication.³¹ This approach is recommended both for patients with prolonged hospital stays postoperatively or day cases that go home immediately after surgery. Utilizing agents that target different mechanisms along the pain pathway will allow for improved analgesia.³¹ In the following section, we outline commonly used analgesic therapies in the perioperative period. It is recommended that these options are used in combination and tailored to the specific patient characteristics such as coexisting medical conditions as well as institutional resources. Of note, patients with chronic pain on analgesic medications should continue the basal analgesia throughout the surgical period and will require interdisciplinary care (e.g., anesthesiologists

Table 2. Perioperative Pain Management Considerations and Recommendations

Preoperative
Preoperative evaluation Identification of risk factors Consider referral to Acute Pain Service or Transitional Pain Service
Intraoperative
Consider regional anesthetic technique (single-shot or continuous catheter) for patients/procedures at high-risk of postoperative pain Consider neuraxial technique, with possible intrathecal opioids Intraoperative lidocaine or ketamine infusions
Postoperative
Comprehensive daily pain assessments Mild pain/Minor surgical procedure Acetaminophen 500–1000 mg PO every 6 h for 3–5 days <i>and one of the following</i> Celecoxib 100–200 PO BID for 3–5 days Ibuprofen 200–800 mg PO BID every 4 h for 3–5 days Naproxen 250–500 mg PO BID for 3–5 days <i>(If cannot take oral medications)</i> Acetaminophen 1000 mg IV every 6 h (if available) for 3–5 days Ketorolac 15 mg IV every 8 h for 3 days <i>In addition to one of the following:</i> Oxycodone 5–10 mg PO every 4 h as needed Hydromorphone 1–2 mg PO every 4 h as needed Morphine 5–15 mg PO every 4 h as needed Moderate pain/Invasive surgical procedure Options in order of increasing difficulty in managing pain 1. Standing Acetaminophen and NSAIDs (if possible) 2. Consider Patient Controlled Analgesia 3. Consider postoperative regional anesthetic technique 4. Consider Ketamine infusion 5. Consider Lidocaine infusion 6. Consider Cannabinoids 7. Consider Gabapentinoids

BID = twice a day; NSAID = Nonsteroidal anti-inflammatory drug; PO = oral route.

or acute pain service) to modify the basal therapy in addition to adding patient-specific analgesic regimens.

Pharmacological Therapies

Acetaminophen

Acetaminophen is considered one of the cornerstones of multimodal pain management. It was first discovered in the 19th century,³² and since then it has become the most widely used drug in the world.³³ While its mechanism of the analgesic action is not clear, it is believed to exert its action via central and peripheral cyclooxygenase inhibition, modulation of spinal serotonin, endocannabinoid activity, and inhibition of nitric

oxide.³⁴ A recent study concluded that scheduled administration of Acetaminophen had a statistically significant decrease in pain scores at all time intervals.^{35,36} It is available in oral, rectal, and intravenous (IV) forms, with the analgesic effects of rectal acetaminophen lasting longer.^{37–39} The oral and rectal routes have been preferred over IV due to lack of pain during administration. The IV formulation was approved in Europe in 2002, the United States in 2011, and in Canada in 2018.³⁷ Currently, there is limited evidence to suggest one formulation is superior to another.^{40–42} It is important to note that absorption of rectal acetaminophen can vary with absorption from lipophilic-based suppositories being more rapid than from water-based formulations.

The efficacy of perioperative acetaminophen is well-studied. A Cochrane review reported that with a single oral analgesic dose of 975 mg to 1 g, the number needed to treat (NNT) to experience a 50% pain relief over 4 to 6 h after administration is 3.6 (95% CI 3.4 to 4.0).⁴³ Given its high tolerability and low side-effect potential,⁴⁴ acetaminophen is often used as a first-line agent. However, the role of acetaminophen as an opioid-sparing agent is unclear. A recent systemic review of the use of acetaminophen in patients after major surgery who were also using patient-controlled analgesia (PCA) indicated a reduction in morphine consumption of 8.7 mg (95% CI -11.4 to -5.9), after adjusting for baseline opioid consumption.⁴⁵ Joint practice guidelines from the APS, ASRA, and ASA recommend the routine use of acetaminophen postoperatively.²⁴ While they are not clear on whether acetaminophen should be prescribed as a standing dose versus as-needed dose, many institutional practices prescribe standing doses during the in-hospital stay after surgery.

The main concern with acetaminophen is hepatotoxicity mediated through the accumulation of a highly reactive metabolite (N-acetyl-p-benzoquinoneimine [NAPQI]); fortunately, it is rare when given at therapeutic doses (below 4 g/day).⁴⁶ Identifying patients at increased risk for toxicity is important to reduce the dose or avoid acetaminophen all together (e.g., those with cirrhosis, alcohol use, or on P450 inducers such as carbamazepine, phenytoin, rifampin).

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs act by inhibiting the cyclooxygenase (COX) enzyme, which is responsible for the formation of prostaglandins from arachidonic acid and is involved in acute inflammatory pain.⁴⁷ COX is found in two isoforms: COX-1 and COX-2. COX-1 is constantly expressed and plays an essential role in the maintenance of gastrointestinal mucosa, platelet function, and renal perfusion, whereas COX-2 is induced by inflammation.^{44,47} All NSAIDs bind to both COX enzymes, with non-selective NSAIDs (i.e., ibuprofen, naproxen, ketorolac) having a greater affinity for the COX-1 enzyme, whereas COX-2 selective NSAIDs (i.e., celecoxib, rofecoxib) have greater affinities for the COX-2 enzyme (5- to 50-fold greater).⁴⁸

Oral NSAIDs have been shown to be effective in managing acute postoperative pain. The NNT for a single oral dose of common NSAIDs (to produce at least 50% maximum pain relief over 4–6 h) are quite low (i.e., ibuprofen 200 mg: NNT 2.1, diclofenac 50 mg: NNT 2.1).⁴⁴ Both perioperative NSAIDs and COX-2 inhibitors appear to reduce IV morphine consumption by 10 mg of morphine.⁴⁵ Perioperative NSAIDs have also been shown to reduce postoperative nausea, vomiting, sedation, and improve patient satisfaction.^{49,50} Further, there is ample

data to suggest that NSAIDs are more effective analgesics than acetaminophen,^{51,52} and that combination is more effective than a single agent alone.⁵³

There is inconclusive evidence with regard to clinically significant side effects of perioperative use of NSAIDs.⁴⁵ In addition to well-known side-effects of gastric bleeding, thromboembolic events, and renal dysfunction, two specific adverse effects exist within the perioperative period, anastomotic leaks after gastrointestinal surgeries and impaired bone healing after orthopedic surgeries. A meta-analysis (16 studies, 15,242 fractures) evaluating the latter complication demonstrated an increased risk (OR 2.07, 95% CI 1.19 to 3.61) of prolonged or impaired bone healing with NSAIDs use after orthopedic procedures (adult and pediatric).⁵⁴ However, the effect was not identified for low-dose NSAIDs (diclofenac <125 mg/day, ketorolac 120 mg/day) taken for less than 2 weeks, which has been confirmed in additional studies.^{55–57} Nonetheless, spine surgeons have erred on the side of caution and prefer to avoid NSAIDs postoperatively.⁵⁸ Additionally, within patients undergoing colorectal surgery, a meta-analysis (24 studies, n = 31,877) showed an increased risk for anastomotic leaks (OR 1.73, 95% CI 1.31 to 2.29) with the use of NSAIDs.⁵⁹ While there are conflicting data to definitively demonstrate an effect on anastomotic leaks, NSAIDs after gastrointestinal surgeries have been shown to improve the return of bowel function and feeding.⁶⁰ Joint guidelines from the APS, ASRA, and ASA state that there is insufficient evidence to recommend against the use of NSAIDs in orthopedic surgeries, spinal fusions, and colorectal surgery.²⁴

Nonsteroidal anti-inflammatory drugs are a useful adjunct to acute pain management after surgery and should be considered for all patients after surgery, except for patient populations at high risk of adverse events (e.g., elderly, renal dysfunction, gastric ulcers, significant bleeding). COX-2 selective inhibitors have significantly lower upper gastrointestinal complications, no antiplatelet effects, and possibly lower risk of renal effects, allowing it to be considered particularly in elderly patients.^{61–63} Generally, if NSAIDs and COX-2 inhibitors are used, they should be given in their lowest effective dose for only a brief period after surgery (3–7 days).^{57,64}

Gabapentinoids

Gabapentinoids, such as pregabalin and gabapentin, are anti-convulsants that are also a class of analgesic medications. The primary mode of action is inhibition of voltage-gated $\alpha_2\delta$ calcium channels leading to inhibition of neurotransmitter release.³¹ While prior reviews have suggested that gabapentinoids reduce postoperative pain and opioid consumption,⁶⁵ a recently published meta-analysis (281 trials, n = 24,682) showed no

clinically significant effect on postoperative pain control.⁶⁵ While gabapentinoids were associated with lower pain on a 100-point scale, the difference was not large enough to be considered clinically significant. Further, it is important to consider the increased risk of adverse events compared to the minimal opioid-sparing effects.^{66–68} Given an increased number of reported side effects such as visual disturbances and dizziness, the usefulness of these agents in the perioperative setting has been recently questioned.⁶⁹

Ketamine

Ketamine is a dissociative anesthetic and is often used during general anesthesia and for procedural sedation. It produces rapid sedation and analgesia that is mediated through antagonism of the N-methyl-D-aspartate receptors (NMDA).⁷⁰ A 2020 systematic review of randomized controlled trials (RCT) indicated that when ketamine was given as an adjuvant to general anesthesia, there were significant reductions in pain intensity up to 24 h after surgery and reduced opioid consumption for up to 12 h postoperatively.⁷¹ These findings were generally consistent with a prior 2018 Cochrane review, except that the opioid reduction effect was seen up to 48 h.⁷²

Ketamine has been demonstrated to be an effective agent for postoperative pain after a number of surgical procedures including abdominal surgery, orthopedic, spinal, otolaryngologic, and gynecological procedures.⁷³ Ketamine reduces postoperative pain scores at rest up to 72 h after surgery (weighted mean difference [WMD] –1.3, 95% CI –2.4 to –0.2).⁷⁴ Further, ketamine infusions reduced postoperative opioid consumption up to 48 h after surgery (WMD [cumulative morphine consumption] –12.7 mg, 95% CI –18.9 to –6.6) and reduced postoperative nausea and vomiting, which may be related to its opioid-reducing effect.^{73,75–78} Additionally, intravenous ketamine infusions can assist in reducing postoperative pain in opioid-tolerant patients⁷⁹ and those with chronic pain undergoing surgery.⁸⁰ In a prior systematic review, ketamine has been shown to reduce CPSP at the 3rd month.⁸¹

However, ketamine can alter blood pressure, heart rate, and mental status, so administration should be done carefully when performed outside a monitored setting (e.g., surgical ward).⁸² Ketamine is associated with psychotomimetic effects (e.g., hallucinations, nightmares), however, when given intraoperatively, there was no significant increase in these side-effects, particularly if a benzodiazepine is administered.⁷¹ Typical infusion regimens range from 0.02 to 0.1 mg/kg/h (any dosage below <0.25 mg/kg/h is considered sub-anesthetic), and at these dosages, side-effects are uncommon.^{83,84} Longer infusions (24–72 h) are safe and show increased benefit over shorter infusions. Infusions should be typically administered in collaboration with the hospital Pain

Service or Anesthesia colleagues and should be considered in patients with challenging to manage postoperative pain refractory to opioid management, after major noncardiac surgery (i.e., spine, thoracotomies), and those with a history of chronic pain or opioid tolerance. Ketamine may not be appropriate for day surgical cases and small procedures not associated with intense postoperative pain. More studies will certainly be required to clearly define the role of ketamine for postoperative analgesia.⁸⁵

Intravenous Lidocaine Infusions

Lidocaine is an amide local anesthetic that provides analgesia through antagonism of voltage-gated sodium channels and appears to have anti-inflammatory and anti-hyperalgesic properties.^{86,87} While lidocaine is most often used for local or regional anesthesia, there has been increasing use of intravenous lidocaine in recent years. It has been used to treat chronic pain disorders in an outpatient setting for decades.^{88,89} Enhanced Recovery After Surgery (ERAS) guidelines adopted intraoperative intravenous lidocaine in bowel surgery given data that it improves postoperative pain, opioid consumption, the return of bowel function, and length of hospital stay (current level of recommendation: strong).⁹⁰ A recent Cochrane review of RCTs confirmed an effect on reducing pain scores up to 24 h after surgery as well as a significant reduction in risk of ileus, time to first defecation, postoperative nausea, and opioid consumption (mean difference [MD] 4.52 mg morphine equivalents, 95% CI –6.25 to –2.79).⁹¹ Lidocaine infusions typically start intraoperatively and many centers have migrated to using postoperative infusions for acute pain.⁹²

Despite the widespread use of lidocaine infusions in clinical practice, during and after surgery, there is little guidance on specific indications, ideal infusion regimen (dose and duration), and what monitoring should be performed. Most benefit has been documented within gastrointestinal surgeries—however, most studies have been within this surgical population. In breast cancer surgery, an intraoperative lidocaine infusion appears to reduce the development of CPSP.^{93,94} Postoperative lidocaine infusions should be considered in patients with refractory acute pain not responsive to opioid therapy, abdominal surgeries, and history of chronic pain. Typical lidocaine infusion dosages include a bolus of 1–1.5 mg/kg followed by a 1–3 mg/kg/h infusion; bolus dose can be omitted if the infusion is expected to continue for hours to days.⁹¹ Monitoring for possible local anesthetic toxicity should be performed, however, at the specified infusion regimens, toxicity is rare.⁹⁵ Toxicity ranges from mild-to-severe adverse effects in a dose-dependent relationship. Mild symptoms include perioral paraesthesia, visual disturbances, tinnitus, sedation, with severe toxicity resulting in cardiovascular collapse and seizures. Thus, monitoring for mild symptoms with cessation of an infusion can prevent progression to severe toxicity. Some institutions

measure plasma lidocaine concentrations (toxicity occurring above 5 µg/mL),⁸⁶ as an extra safety mechanism, although this is not done routinely.⁹⁶ Toxicity is treated with lipid emulsion (e.g., Intralipid®). The use of Intralipid (lipid emulsion) as a treatment of local anesthetic toxicity (LAST) has become a standard of care. It is a lipid emulsion that acts as a lipid sink to draw the hydrophobic local anesthetics out of the tissues. The American Society of Regional Anesthesia has published specific recommendations and a checklist for the treatment of LAST.

Cannabinoids

Cannabinoids are substances that act on the cannabinoid CB1 and CB2 receptors. CB1 receptors are found predominately in the brain and spinal cord (along the pain pathways), whereas CB2 receptors are primarily found on immune cells.⁹⁷ Two categories of cannabinoids exist, cannabis-derived pharmaceuticals (i.e., dronabinol and nabilone) and botanical-derived extracts. Analgesic

efficacy of cannabinoids has been primarily demonstrated in chronic pain patients,^{98–101} with little literature on perioperative use. A recent systematic review of RCTs (924 patients) and observational studies (4259 patients) on the use of cannabinoids for acute pain in the perioperative period indicated no significant reduction in opioid consumption but a significant increase in pain at 12 h after surgery and increased odds of hypotension.¹⁰² Considering the current evidence base, there are no strong indications to use cannabis in the perioperative period.

Opioids

Opioids are considered as a central component of postoperative pain management (Figure 1). Opioids exert their action by binding to opioid receptors (e.g., mu, delta, and kappa), which are located on the central and peripheral nervous system. The mu receptor is primarily involved in providing analgesia; however, mu receptors are also expressed on the gastrointestinal tract and

Procedure	Range (minimum–maximum)
General surgery	
Laparoscopic cholecystectomy (procedure 1)*	0–10
Laparoscopic inguinal hernia repair, unilateral (procedure 2)*	0–15
Open inguinal hernia repair, unilateral (procedure 3)*	0–10
Open umbilical hernia repair	0–15
Breast surgery	
Partial mastectomy without sentinel lymph node biopsy (procedure 4)*	0–10
Partial mastectomy with sentinel lymph node biopsy (procedure 5)*	0–15
Thoracic surgery	
Video-assisted thoracoscopic wedge resection	0–20
Orthopaedic surgery	
Arthroscopic partial meniscectomy	0–10
Arthroscopic ACL/PCL repair	0–20
Arthroscopic rotator cuff repair	0–20
ORIF of the ankle	0–20
Gynecologic surgery and obstetric delivery	
Open hysterectomy	0–20
Minimally invasive hysterectomy	0–10
Uncomplicated cesarean delivery	0–10
Uncomplicated vaginal delivery	0
Urologic surgery	
Robotic retropubic prostatectomy	0–10
Otolaryngology	
Thyroidectomy, partial or total	0–15
Cochlear implant	0
Cardiac surgery	
Coronary artery bypass grafting	0–20
Cardiac catheterization	0

Figure 1. Opioids as a central component of postoperative pain management.

may be involved in causing opioid-induced nausea, vomiting, and constipation. Opioids can be administered via oral, rectal, sublingual, transdermal, subcutaneous, intramuscular, intravenous, or neuraxial routes. The most commonly used drugs after surgery for in-patient acute pain are oxycodone, morphine, and hydromorphone in Canada,^{103,104} although the most frequently prescribed opioids in the US was oxycodone with acetaminophen and hydrocodone with acetaminophen, and those in the UK was morphine and codeine with acetaminophen.¹⁰⁵ After a major surgery, opioids are typically delivered via patient-controlled analgesia (IV PCA), which allows patients to control their opioid administration while reducing the risk of overdose and can also reduce nursing workloads,¹⁰⁶ facilitate early ambulation, reduce respiratory complications, and provide higher patient satisfaction.¹⁰⁷

Although opioids have a diverse range of side-effects (Table 3), life-threatening adverse events, such as respiratory depression, are rare and typically happen within 24 h after surgery under intravenous patient-controlled or neuraxial analgesia.¹⁰⁸ A systematic review of observational studies reported the incidence of postoperative opioid-induced respiratory depression of 5 in 1000.¹⁰⁹ Also, those with pre-existing cardiac disease, pulmonary disease, and obstructive sleep apnea are at increased risk of opioid-induced respiratory depression.

Surgery is a period where opioid-naïve patients become exposed to opioids. Unfortunately, up to 6.5% of patients after

minor and major surgery develop new persistent opioid use.¹¹⁰ Tobacco use, alcohol and substance abuse disorders, mood disorders, anxiety, and preoperative pain are risk factors for persistent use. Opioid prescribing after surgery, and particularly at discharge appears to be an important factor—45% of patients who do not take opioids on their last day in the hospital after surgery are prescribed opioids upon discharge.¹¹¹ Further, patients only used 27% of the opioids prescribed to them after surgery and prescription size was the strongest predictor of long-term opioid use.¹¹² A multidisciplinary expert panel (composed of surgeons, pain specialists, pharmacists, patients) at John Hopkins provided consensus recommendations on the appropriate opioid prescribing after different surgical procedures. Recommendations for prescribing for most surgeries include 0 to 15 tablets of oxycodone 5 mg, with only certain surgeries (thoracic, orthopedic, open gynecological surgeries) allowing up to 20 tablets. A Canadian consensus statement on recommendations for opioid prescribing after surgery has also been published and includes a number of recommendations including (in part) patient education about appropriate expectations and non-opioid analgesia use, identification of risk factors, basing opioid prescription on functional recovery after surgery, prescription having an expiry date of 30 days from discharge, and if a refill is needed, only providing a 14-day refill.⁵⁷

Interventional Pain Procedures

Regional anesthesia involves using local anesthetics to produce a conduction block at specific neuronal tissues. Patients may receive a regional anesthetic as their primary form of anesthesia during surgery or to assist with postoperative pain. These procedures are typically performed under ultrasound-guidance, which may reduce complications compared to traditional landmark-based approaches.¹¹³ Literature on the efficacy of regional anesthesia after surgery varies on the type of procedure and specific technique, but overall, these procedures have been shown to result in improved postoperative analgesia and reduced opioid consumption.^{114–116} A large number of regional techniques are used perioperatively and include epidural anesthesia/analgesia (cesarean sections and midline laparotomies), brachial plexus blocks (i.e., interscalene, supraclavicular, infraclavicular, axillary brachial plexus blocks for upper extremity procedures), fascial iliac plane block (for hip surgery), adductor canal block (used in knee surgeries), and erector spinae block (for mastectomy or truncal surgeries).¹¹⁷ The length of the effect depends on the type of local anesthetic and whether the procedure is a “single-shot” (12 to 24 h) or includes placement of a catheter, which allows for continuous infusion of local anesthesia (several days after surgery).^{118,119} Further, the combination of multiple regional blocks appears to provide superior analgesia compared to

Table 3. Common Opioid-Related Side-Effects

Common	Occasional	Rare
Gastrointestinal		
<ul style="list-style-type: none"> • Nausea • Vomiting • Constipation 	<ul style="list-style-type: none"> • Delayed gastric emptying 	<ul style="list-style-type: none"> • Biliary colic
Neurological		
<ul style="list-style-type: none"> • Sedation • Drowsiness • Cognitive dysfunction 	<ul style="list-style-type: none"> • Hallucination • Mood disturbance • Anxiety • Myoclonus 	<ul style="list-style-type: none"> • Delirium • Seizure • Addiction
Respiratory		
<ul style="list-style-type: none"> • Cough reflex inhibition 	<ul style="list-style-type: none"> • Dry mouth • Bronchospasm 	<ul style="list-style-type: none"> • Respiratory depression • Noncardiac pulmonary edema
Others		
<ul style="list-style-type: none"> • Miosis 	<ul style="list-style-type: none"> • Pruritis • Muscle rigidity 	<ul style="list-style-type: none"> • Hyperalgesia • Allodynia • Tolerance • Physical dependence

single-injection techniques.¹²⁰ Furthermore, for certain surgical populations, such as hip fracture patients, early regional techniques should be considered as they will typically be in pain prior to their surgical procedure. A study in patients admitted with hip fractures indicated that a preoperative fascia iliaca nerve block resulted in lower preoperative opioid consumption, lower pain intensities, and earlier discharge.¹²¹

Several factors discourage the use of regional anesthesia, such as lack of clinical experiences or resources and, access to an ultrasound machine which is considered standard-of-care in performing regional anesthesia. Of note, regional anesthesia technique and timing (i.e., when to perform, if a catheter can be placed, when to remove catheter) is also dependent if the patient is on anticoagulation or antiplatelet therapy or has a bleeding disorder.¹²² In general, peripheral nerve blocks may be considered in patients with anticoagulation/antiplatelet therapy, whereas neuraxial techniques are contraindicated (i.e., due to risk of epidural hematomas causing spinal cord or nerve root compression).

Patients with Chronic Pain Presenting for Surgery

Patients with a history of chronic pain are more likely to experience moderate-to-severe pain after surgery.¹²³ These patients may also be maintained on chronic opioids which presents further challenges within the perioperative period. These patients are not only at higher risk of more severe pain and greater opioid use after surgery, but epidemiological studies also indicate that they are at higher risk of poor postoperative outcomes—in a cohort of 200,005 patients undergoing elective surgery, preoperative opioid use was associated with a longer hospital stay, higher rate of readmission, and increased healthcare expenditures.¹²⁴

Multidisciplinary perioperative care models such as the Transitional Pain Service have been developed to manage these high-risk patients. These programs typically evaluate patients prior to surgery, mitigate exacerbating factors, provide interdisciplinary care including behavioral management strategies, and support care after discharge.^{125,126} In general, patients on long-term non-opioid analgesics should have their medications continued in the perioperative period, with some exceptions such as NSAIDs in surgery at high-risk of bleeding. Further, patients on chronic opioids should be continued on their home doses in the perioperative period, while anticipating greater opioid consumption after surgery (up to three times greater) compared to opioid-naïve patients.¹²⁷ Long-acting opioid formulations such as buprenorphine should also be continued perioperatively, as suggested by Canadian expert consensus.¹²⁸ Opioid-tolerant patients should be maximized on non-opioid adjuncts, interventional regional techniques, and particularly ketamine infusions, which has been shown to reduce pain

intensities and opioid consumption in those with chronic opioid use.^{79,129} In challenging cases, opioid rotation (changing from one opioid to another) can potentially be helpful in the postoperative period, which takes advantage of the incomplete cross-tolerance of opioids.¹³⁰ High-risk patients such as those with a preoperative history of chronic pain and those maintained on chronic opioids should likely be followed after hospital discharge for titration back to baseline analgesic and opioid dosages.

Conclusions

Postoperative pain is an important consideration in a patient's perioperative care. Unmanaged pain may contribute to poor postoperative clinical outcomes, including CPSP which is analogous to a functional disability associated with increased healthcare expenditures. Optimal management of postoperative pain includes multimodal and interdisciplinary approaches with the utilization of effective therapies in the preoperative, intraoperative, and postoperative periods.

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