Strategies for Optimizing Perioperative Pain Management for the Cancer Patient

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KEYWORDS

• Cancer pain • Pain management • Total pain • Postoperative pain

KEY POINTS

- Acute postoperative pain in a patient with cancer must be distinguished and managed differently from chronic cancer-related pain.
- "Total pain" is an important concept that underscores the importance of a bio-psychosocial approach to the management of pain in patients with cancer.
- Management of acute postoperative pain starts with education and expectation setting in the preoperative period.
- A multimodal approach to perioperative pain management should be used whenever possible.
- Surgeons must be mindful of the risk of new persistent opioid use developing in the post-operative period.

INTRODUCTION

Background

Pain in the population of patients with cancer is unique. It is characterized by multimorphism: by a physical nature classified by etiology, temporality, location, and time and by a psychological nature, with emotional, cognitive, and behavioral factors that impact pain. Psychological factors may increase the perception of pain, whereas improper pain control may also trigger psychological distress.[1] Pain syndromes in the patient with cancer can be broken down into those arising from the direct effect of neoplasm on nearby tissues (85%), the side effects of a cancer treatment (17%), disease progression (9%), and other causes not directly related to malignancy.[2] The

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etiology of pain in a patient with cancer may vary at any given moment, from cancer-related chronic pain to acute surgical pain. Acute surgical pain may have some overlapping characteristics with chronic cancer pain. However, distinguishing these two is important, as the difference in expected chronicity impacts treatment strategies. We focus on management of acute surgical pain in the patient with cancer.

Prevalence

Pain impacts a large proportion of our population of patients with cancer. Pain prevalence averages 53% across the cancer continuum, from diagnosis through survivorship or end of life, and 38% of those patients define their pain as moderate to severe pain.[3,4] Chronic postsurgical pain, defined as pain related to a procedure persisting more than 2 to 3 months after surgery, continues to increase in the population of patients with cancer as survival outcomes improve.[5] The concept of "total pain" is an important one as it relates to the population of patients with cancer. "Total pain" includes sources of pain that are nonphysical (anxiety, rage, depression, interpersonal interactions, family strains, nonacceptance of caregivers, doubting faith, sense of hopelessness) and underscores the importance of a biopsychosocial approach to the management of pain in patients with cancer, whether it is acute postoperative pain or chronic cancer-related pain.[6]

Clinical Impact of Cancer-Related Pain

Proper management of cancer pain impacts our patients' quality of life and willingness to receive other disease-directed therapy.[3] One-sixth of patients with cancer have depression and one-quarter have other mood disorders while actively receiving treatment for their cancer. Major depression is associated not only with pain but also with a decrease in adherence to treatment, longer hospital stays, and increased suicide rates in patients with cancer.[3] The perioperative period is characterized by the surgical stress response, angiogenesis, and immunomodulation that may support tumor spread.[7] It has been suggested that managing pain in the immediate perioperative period provides an opportunity to modulate the consequences of the stress response on the immune system and potentially mitigate cancer spread.[7] Pain also has important socioeconomic implications, with increased health care costs and decreased productivity.[8]

This review focuses on preoperative, intraoperative, and postoperative strategies for management of perioperative pain in the patient with cancer, with specific attention to approaches centered on optimizing quality of life. We conclude by addressing pain in special populations, including patients with preoperative opioid use and those with a history of substance abuse, as well as pain control near the end of life.

PREOPERATIVE PAIN MANAGEMENT OF THE PATIENT WITH CANCER

Understanding mechanisms of cancer-related pain and expectation setting are integral to preoperative counseling with patients. Mechanisms of cancer-related pain likely include tissue destruction from tumor production of proteases, stimulation of cytokine secretion, and immune cell migration and nerve growth by substances produced by cancer cells. Once this occurs, it is thought that neuromodulators are released, leading to sensitization and activation of peripheral neurons, and overexpression of nociceptive mediators in the spinal cord. The result is increased pain signaling in patients with cancer.[9] Pain, however, is not necessarily proportional to tumor burden. It therefore must be understood by the patients that surgery with the objective of reducing (or even completely resecting) cancer burden may not resolve

or even necessarily improve their pain. Moreover, as discussed in the introduction, total pain involves physical, psychological, and social components that are best addressed by a multidisciplinary approach with multimodal treatment strategies that should be initiated in the preoperative period.

Preoperative education that is age-appropriate and considers the individual patient's health literacy, cultural and linguistic competency, and allows adequate time for questions, should underscore the goals of postoperative pain management.[10] The idea of focusing on function when assessing postoperative pain management should be introduced preoperatively. Patients should be counseled, depending on the planned surgery, that they are unlikely to be pain free in the early postoperative period, and that the goal will be to keep the pain tolerable enough that it is not interfering with their function, particularly with respect to the things they need to do to recover (like sleep, eat, and ambulate). Individually tailored education programs for patients with increased needs (including medical comorbidities) are associated with reduced postoperative opioid consumption, less preoperative anxiety, fewer requests for sedatives, and reduced length of stay after surgery.[10] Special attention also must be given to those with opioid consumption before surgery, as addressed in the special populations section later in this article.

Preoperative evaluation including a detailed history of the patient's medical and psychiatric comorbidities, medications, and history of chronic pain, substance abuse, and previous postoperative responses to pain management will also help guide the postoperative pain management planning.[10]

INTRAOPERATIVE PAIN MANAGEMENT OF THE PATIENT WITH CANCER

Approach

Although intraoperative pain management is primarily the purview of our anesthesia colleagues, it behooves the surgeon to have some degree of familiarity with modalities used that help reduce postoperative nausea and vomiting, length of stay, and intensity of pain that might contribute to higher volume opioid consumption.[11]

Comprehensive coverage of Enhanced Recovery After Surgery (ERAS) protocols and their clinical impact is beyond the scope of this review but it should be noted that ERAS, although not unique to the population of patients with cancer, has resulted in shorter length of hospital stays, reductions in complications, and reduced readmissions and hospital costs.[12] Implementation of ERAS protocols have improved outcomes in almost all major surgical specialties and should be considered in the provider's approach to managing perioperative pain in the patient with cancer.

Pharmacologic Interventions

Modalities to improve perioperative pain control in the intraoperative setting include use of regional anesthesia, use of opioid-sparing anesthesia (including nerve blocks), balancing fluids, and maintaining temperature control. The emphasis of ERAS is on maintaining homeostasis and reducing the stress response.[12]

Several nerve blocks have been used by anesthesiologists, which depending on the procedure, might include thoracic paravertebral nerve block, transversus abdominis plane block, quadratus lumborum block, or neuraxial neurolytic blocks. Neuraxial neurolysis provides analgesia by blocking sensory fibers (A-delta and C-fibers) while preserving motor fibers, which serves patients with cancer willing to participate in physical rehabilitation especially well.[13] Intrathecal morphine was evaluated in a meta-analysis and concluded that it decreases pain intensity at rest and on movement up to 24 hours after major surgery.[14]

POSTOPERATIVE PAIN MANAGEMENT OF THE PATIENT WITH CANCER

Mechanisms and Risks of Chronic Postoperative Pain

The goal postoperatively is to return patients to their preoperative state of pain, if not better. Effectively managing postoperative pain requires an understanding of the pathophysiology and the potential for transition from acute to chronic pain.

Surgical trauma causes damage and inflammation, which leads to peripheral and then central sensitization. First, the surgical trauma activates and sensitizes C and A-δ fibers in the periphery, which releases glutamate and increases expression of sodium channels. Glutamate then activates iGlu (ligand-gated ionotropic receptors) and mGlu (G-protein couple metabotropic receptors). The progression from acute to chronic postsurgical pain may result from the activation of these iGlu receptors.[5] The exact mechanisms of postsurgical pain are not fully understood, and other suggested mechanisms involve pathophysiological changes related to long-term potentiation, activated microglial cells and astrocytes, chemokines, toll-like receptor 4 upregulation, increased spontaneous impulse discharges, reduced thresholds, loss of GABAergic descending modulation, protein kinase mediation, and expression of cathepsin G as a pronociceptive mediator.[5]

There are many risk factors for the development of chronic postsurgical pain (pain that persists for more than 2–3 months following surgery).[5] Preoperative pain and poorly managed acute perioperative pain are the 2 risk factors with the strongest correlation. Other risk factors include younger age, body mass index greater than 30, lower education level, type of surgery (with thoracotomy, breast, amputation, and hernia having higher associations), and chemotherapy and/or radiotherapy at any point during cancer treatment.[5] Considering total pain, psychological factors such as anxiety, depression, posttraumatic stress disorder, recall of perioperative pain, emotional function, and vulnerability all place a patient at higher risk of chronic postsurgical pain. Protective factors may include marriage, full-time employment, alcohol consumption, and cigarette smoking but their real effects remain unclear.[5]

Postoperative Pain Assessment

Pain assessment should be comprehensive and include pain characteristics, mechanisms, location, current analgesic treatment, and impact on function. Validated pain intensity assessment scales include the numerical rating scale, verbal rating scale, visual analog score, pain thermometer, and faces rating scale. However, postoperative pain assessment should not rely too heavily on pain intensity assessment scales because cancer pain is a multidimensional experience.[15] Judgment of adequacy of pain control should at least include, if not focus primarily on, impact of pain on function and ability to recover from surgery.

Pharmacologic Interventions

There is significant overlap in the pharmacologic modalities used for acute perioperative pain and chronic cancer-related pain. However, it is critical to maintain a distinction between the two when making a pain management plan, as the chronicity of the two differ, as does the role of opioids and appropriateness of long-term opioid use. Although a familiarity with some tenants of chronic cancer pain management may help the surgeon contextualize preoperative cancer-related pain, this section focuses on the management of acute surgical pain with the goal of returning the patient to their preoperative baseline (in terms of both pain and pain medication use). Medications used in the postoperative setting and their efficacies are briefly discussed here, with doses listed in **Table 1**.

Table 1
Medications with route of administration and dosing

Medication	Route of Administration	Starting Dose	Titration
Ibuprofen[52]	Oral, IV	Oral: 200–800 mg 3–4 times daily IV: 400–800 mg every 6 h PRN	Max dose: 3200 mg/d
Paracetamol[52]	Oral, IV, Rectal	Oral: 325–650 mg q4-6h or 1g q6h PRN IV: 650 mg q4h or 1g q6h Rectal: 325–650 mg q4–6h PRN	Max dose: 4 g/d Rectal max dose: 3.9 g/d
Morphine[53]	Oral, IV, IM (not recommended), Rectal, PCA	Oral: 10 mg q4h IV: 1 to 4 mg q1–4h PRN Rectal: 10 mg q4h PCA: 0.5 to 2 mg q5–10m	Oral: up to 30 mg q4h PRN IV: up to 10 mg q4h PRN PCA: Max dose 7.5 mg in 1 h, or 30 mg over a 4-h period
Oxycodone IR[54]	Oral, Rectal	Oral: 5–15 mg q4-6h Rectal: one suppository 3–4 times QD PRN	Titrate to appropriate effect
Oxycodone ER[54]	Oral	Oral tablet: 10 mg q12 h Oral capsules: 9 mg q12 h	Adjust dose in increments (25% to 50%) no more frequently than q1–2d (max 288 mg/d)
Hydrocodone[55]	Oral	Oral: 20 mg QD Zohydro: 10 mg q12 h	Increase 10–20 mg q3–5d Zohydro: 10 mg q12 h q3–7d ≥80 mg only in pts who are opioid tolerant
Hydromorphone[56]	Oral, IV, IM (not recommended), SubQ, PCA	Oral: 2 to 4 mg q4–6h PRN (tablets) or 2.5–10 mg q3–6h PRN (oral solution) IV: 0.2 mg to 1 mg q2–3h PRN SubQ: 1 to 2 mg q2–3h PRN PCA: Demand dose 0.1–0.4 mg q10 m	Titrate higher end of ranges for desired effect, opioid-tolerant patient may need higher initial dosing
Gabapentin[29]	Oral	300 mg to 1.2 g as single dose, 1–2 h before surgery or immediately following surgery	Prolonged use for neuropathic pain (range 300 mg TID to 1.2 g TID)
Pregabalin[29]	Oral	75–300 mg as single dose 1 h before surgery	Prolonged use for neuropathic pain (initial 25–150 mg/d in 2–3 divided doses, can increase 25–150 mg/d to a usual dose of 300–600 mg/d in 2–3 divided doses)

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Table 1
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Medication	Route of Administration	Starting Dose	Titration
Amitriptyline[31]	Oral	25 mg QHS (days −7 to −5 preoperatively), 50 mg QHS (days −4 to −3 preoperatively), 75 mg QHS (days −2 to −1 preoperatively)	N/A for surgical pain
Desipramine[31]	Oral	25 mg QHS (−7 to −5 preoperatively), then 50 mg QHS (days −4 to −3 preoperatively), 75 mg QHS (days −2 to −1 preoperatively)	N/A for surgical pain
Fluoxetine[31]	Oral	10 mg QHS for 7 d preoperatively	N/A for surgical pain
Lidocaine[34]	IV	10 mg or 1–3 mg/kg	Infusion of 1–5 μg/kg per h or 2-4 mg/min
Esmolol[35]	IV	Loading dose: 30–60 mg	Infusion of 5–500 μg/kg per min
Caffeine[36]	Oral	100–130 mg	N/A for surgical pain

Abbreviations: ER, extended release; IM, intramuscular; IR, immediate release; IV, intravenous; N/A, not applicable; PCA, patient-controlled analgesia; PRN, as needed; q, every; QD, every day; QHS, quaque hora somni (every evening); SubQ, subcutaneous; TID, 3 times a day.

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to function both peripherally and centrally in nociception by blocking prostaglandin production.[16] NSAIDs should be considered for all surgical procedures because they decrease opioid requirements, improve patient satisfaction, decrease recovery times, and decrease morbidity in the postoperative period.[16] A Cochrane review examined evidence for NSAIDs or paracetamol, alone or combined with opioids, in treating chronic cancer pain. The studies in the review were small and of poor quality, so the conclusion drawn was that the impact of using an NSAID alone for chronic cancer pain is unknown.[17] Despite the lack of evidence in specifically treating chronic cancer pain, NSAIDs should be used in managing postoperative pain in the patient with cancer.

Paracetamol (acetaminophen)

A review of 14 studies containing 1129 patients compared the efficacy of a combination of paracetamol with an NSAID, versus an NSAID alone in the acute postoperative period.[18] The review suggested that combining the two conferred additional pain control over either drug alone.[18] With regard to chronic cancer pain, a Cochrane review found no convincing evidence of paracetamol being different from placebo in improving quality of life, use of rescue medication, or participant satisfaction.[19] This supports the use of paracetamol in acute surgical pain, but not necessarily in chronic cancer pain.

Opioids

Opioids act by blocking pain receptors. Two commonly used opioids, morphine and oxycodone, act by blocking the μ receptor and κ receptor, respectively.[20] The oral

bioavailability and potency of oxycodone is greater than that of morphine and has been shown to be more effective at blocking visceral pain, which may provide an added benefit when treating postsurgical pain.[20] A review of 26 clinical trials concluded that oral oxycodone had superior postoperative analgesic efficacy compared with placebo in patients undergoing a variety of surgeries, including laparoscopic cholecystectomy, abdominal or pelvic surgery, bunionectomy, breast surgery, and spine surgery.[20]

An individual approach should be implemented when prescribing opioids and should include whether the patient is opioid-naïve to determine the starting dose, frequency, and titration. The short half-life of opioid pure agonists (morphine, hydromorphone, fentanyl, and oxycodone) are preferred because they are easier to titrate than long half-life opioids (methadone, levorphanol).[21]

Persistent Opioid Use and Dose Reduction Postoperatively

Because surgery is an acute pain event, monitoring for postoperative opioid dose tapering should occur even in the population of patients with cancer. Opioids should be prescribed judiciously, with an understanding with the patient that the goal within a few weeks after surgery, is to have the patient return to his or her preoperative levels of opioid use (off opioids altogether if the patient was opioid-naïve at time of surgery). Opioids prescribed during and after surgery may beget long-term opioid use regardless of whether a patient is opioid tolerant or has had prior exposure to opioids.[22] More than 60% of people receiving 90 days of continuous opioid therapy postoperatively remain on opioids years later. Patients receiving an opioid prescription after short-stay surgeries have a 44% increased risk of long-term opioid use compared with those who did not receive an opioid prescription.[22] Measures to shorten duration of postoperative opioid use are necessary to limit the transition from acute to long-term opioid use.[22] Risk factors for chronic opioid use after surgery among opioid-naïve patients include male sex, age older than 50 years, preoperative use of benzodiazepines, preoperative use of antidepressants, depression history, and alcohol and drug abuse history.[22] Reduction of persistent opioid use involves multimodal analgesia (2 or more medications or nonpharmacologic interventions that often include gabapentinoids, acetaminophen, ketamine, NSAIDs, and regional anesthesia).[22] The standard of care is to advise patients to discontinue opioids when they no longer have pain, but a disconnect between opioids prescribed and opioids used after surgery exists, and patients usually self-taper with minimal instructions after surgery.[22]

Historically, physicians have overprescribed opioids. Alarmingly, 45% of patients who did not take opioids on their last day of surgical hospitalization were prescribed opioids at discharge.[23] Weston and colleagues[24] described a cohort of 108 patients who received a minimally invasive hysterectomy, in whom 79% had cancer. The median prescribed opioids were 30 pills, but median use was 10 pills. Mark and colleagues[25] performed a case-control study that included 1231 patients undergoing major gynecologic oncology surgery. The intervention group received an opioid-restrictive protocol, with patients prescribed no more than 3 days of opioids.[25] Mean opioid pill prescriptions went from 43.6 pills for open surgery and 38.4 pills for minimally invasive surgery to 12.1 and 1.3 pills, respectively. This intervention did not change postoperative pain scores, patient satisfaction, or refill requests, suggesting that a reduction in prescribed opioids is safe and attainable.[25]

New, persistent opioid use, defined as receiving an additional opioid prescription between 90 and 180 days after surgery, remains an issue in both the noncancer and cancer population postoperatively.[26] In a review of 68,463 patients undergoing curative-intent surgery who filled opioid prescriptions, 10.4% of opioid-naïve patients

experienced new, persistent opioid use. One year after surgery, these patients continued to fill prescriptions to doses similar to chronic opioid users.[26]

Procedure-specific prescribing recommendations may help reduce the common overprescribing issue.[23] An expert panel consensus developed outpatient opioid prescribing ranges for 20 common surgical procedures in 8 surgical specialties, and although not specific to the cancer population, these may serve as a guideline in managing opioid prescriptions postoperatively.[23]

In addition to their time-limited role in postsurgical pain, according to the National Comprehensive Cancer Network (NCCN), opioids are one of the cornerstones of chronic cancer pain management.[21] The appropriate dose of opioid is based on the patient's pain intensity and treatment goals. The NCCN recommends considering opioid rotation (switching from one opioid to another) if pain is inadequately managed despite dose titration, or there are persistent adverse effects, change in condition (unable to tolerate oral medications), or restrictions due to cost or insurance coverage.[21]

Side effects of opioids are common and include constipation, nausea and vomiting, pruritus, delirium, respiratory depression, motor and cognitive impairment, and sedation. These side effects must be managed, as these physical symptoms can contribute to the total pain of the patient with cancer but also provide another reason to wean opioid use to that of the presurgical state.[27]

GABAPENTIN AND PREGABALIN

Gabapentin and pregabalin are both antiepileptics that bind to voltage-dependent calcium channels, which are found in the spinal cord. The action of these drugs inhibits the release of excitatory neurotransmitters and reduces glutamate availability at NMDA receptors. Pregabalin has analgesic, anxiolytic, and anticonvulsant activity and is 6 times more potent than gabapentin.[28] A review of the literature suggests that when neuropathic mechanisms of pain predominate, physicians should consider using a low-dose adjuvant, with the best evidence supporting use of gabapentin.[29] Their utility in postoperative pain and reduction of opioid consumption has also been researched, with numerous meta-analyses indicating their efficacy.[30] However, a more recent meta-analysis of 97 studies cautioned against their use given the risk of serious adverse events and only a modest opioid-sparing effect, and a different meta-analysis showed that pregabalin did not prevent development of chronic postsurgical pain.[30]

Observational studies have shown that neuropathic pain is found in 35.9% to 39.7% of patients with chronic cancer pain, suggesting that gabapentinoids can play a role in cancer pain separate from postsurgical pain.[29] Detailed discussion of gabapentinoid use for chronic cancer pain is outside the scope of this paper.

ANTIDEPRESSANTS

Tricyclic antidepressants, including amitriptyline and desipramine, are commonly used for various chronic pain conditions and have also been evaluated in a limited number of studies for acute postoperative pain. Only one study with amitriptyline showed significantly lower pain intensity at 24 hours postoperatively.[31] Desipramine showed promise when administered several days before surgery in 2 separate studies.[31] However, these studies were not specific to the patient with cancer and ultimately the limited evidence available does not support their use in the management of postoperative pain.[32]

Selective serotonin reuptake inhibitors and serotonin norepinephrine reuptake inhibitors were also evaluated for their clinical use in the postoperative setting. Fluoxetine

showed no improvement over placebo in reducing opioid use.[31] In a group of patients undergoing mastectomy, venlafaxine was administered the evening before surgery and for the first 10 postoperative days. Pain with movement and use of postoperative analgesics were reduced in the venlafaxine group.[31] There remains limited available evidence to strongly suggest that duloxetine provides an opioid-sparing effect.[32]

LOCAL ANALGESICS

Lidocaine is commonly used for neuraxial and peripheral nerve blocks but also has analgesic properties when administered intravenously. Suggested mechanisms of action include decreased release of proinflammatory cytokines, nuclear factor-kB-modulated downregulation at the mRNA level, and inhibition of NMDA receptors.[33] A 2015 Cochrane review containing 43 randomized controlled trials compared intravenous lidocaine to placebo and concluded that a bolus of lidocaine (10 mg or 1 to 3 mg/kg), followed by an infusion (1 to 5 mg/kg per hour or 2 to 4 mg/min) reduced pain scores at 1 to 4 hours and 24 hours after surgery. It also decreased perioperative opioid requirements, decreased postoperative nausea, vomiting, and ileus, and shortened hospital length of stay by 8 hours.[34]

ESMOLOL

Esmolol is a selective β-1 blocker with rapid onset and offset. Given intravenously, its mechanisms of action in control of postoperative pain are speculative, but possibly include a blockade of the excitatory effects of pain signaling and modulation of central pronociceptive activity.[32] A meta-analysis concluded that perioperative infusion of esmolol (5–500 μg/kg per minute) with or without a loading dose resulted in lower pain scores, lower postoperative opioid consumption, and decreased postoperative nausea and vomiting. The meta-analysis did conclude that larger trials would need to be conducted given the high risk of bias in the studies reviewed.[35]

CAFFEINE

Caffeine is a methylxanthine, which acts as a central nervous system stimulant to increase wakefulness, endurance, heart rate, blood pressure, and mood.[36] Several studies have reviewed the effect of adding caffeine to analgesics, including paracetamol, aspirin, and ibuprofen for control of postsurgical pain. A Cochrane review recently evaluated 25 comparisons of analgesic plus caffeine versus analgesic alone in a total of 4262 participants.[36] The proportion of participants who achieved at least 50% pain relief was dose dependent: 6% at doses of 65 mg or less, 8% with doses between 70 and 150 mg, and 11% with doses of 150 mg or more. The review concluded that caffeine is effective at doses of 100 mg or more in providing pain relief for an additional 5% to 10% of patients. This was specifically evaluated in the postsurgical population, but little is known about its relief of chronic or nonsurgical pain.[36]

MEDICAL CANNABIS

Cannabinoids are commonly administered via inhalation, orally, or via sprays and have been suggested as modulators of the pain pathway through one of the body's endogenous signaling systems. A study containing 11 patients evaluated the impacts of dose escalation of cannabis extract (5, 10, or 15 mg) on postoperative pain.[37] Less rescue analgesia was requested, and pain intensity was decreased in the group that received 15 mg. However, these patients also experienced greater sedation, more adverse events, and the study was terminated early because of a serious

vasovagal adverse event in a patient receiving 15 mg.[37] The study did conclude that the number needed to treat is equivalent to many routinely used analgesics without frequent adverse effects, but given the paucity of data, more research is needed before a recommendation for perioperative cannabis use can be made.

A review of 5 clinical studies evaluating the effects of cannabinoids on controlling cancer pain found evidence to suggest that medical cannabis use reduces chronic or neuropathic pain in patients with advanced cancer. The reviewers found that many of the studies lacked statistical power and concluded that there remains a need for further double-blind, placebo-controlled clinical trials with larger sample sizes to be able to establish optimal dosage and efficacy of cannabinoid therapy.[38]

SPECIAL POPULATIONS AND CIRCUMSTANCES

Patients with Preexisting Opioid Use

Inadequate pain management is common in patients with preexisting opioid use.[39] Patients taking opioids preoperatively have a higher risk of increased severity and duration of pain after surgery, prolonged postoperative opioid use, increased hospital length of stay, and postoperative complications. Providers must understand clinical phenomena that occur in patients with chronic opioid use, including tolerance, physical dependence, hyperalgesia, withdrawal, and addiction. Preoperative referral to an addiction specialist or to an acute pain service may also be warranted.[39]

Chronic opioid use causes central sensitization, which leads to increased severity of acute and chronic pain due to altering of signaling pathways. The preoperative evaluation should include differentiating between opioid use and abuse, evaluating for coexisting psychiatric disorders, avoiding biases, and gathering a comprehensive understanding of the patients' fears. There is insufficient evidence to decrease or discontinue opioids preoperatively, but it is helpful to develop a pain treatment plan.[39]

Several studies have suggested that opioid-dependent patients have fourfold increased opioid requirements in the postoperative period compared with those who are opioid-naïve.[40] Multimodal analgesia is particularly critical in these patients, including consideration of use of regional anesthesia and patient-controlled analgesia (PCAs). Advantages of PCAs in this patient population include maintaining stable plasma levels, pain relief with lower total opioid consumption, and fewer interactions between health care providers, which reduces patients' anxiety, prejudices, and acute withdrawal episodes.[40]

Ketamine is supported for postoperative pain control in opioid-tolerant patients.[41] Ketamine, by blocking NMDA receptors, can prevent central sensitization and inhibit wind-up phenomenon, opioid-related tolerance, hyperalgesia, and has shown improved pain control and reduction in opioid consumption postoperatively. There were no clear differences in adverse effects when using ketamine.[41] It may be helpful to involve anesthesia or pain specialist colleagues if considering ketamine use in patients with otherwise refractory perioperative pain.

Patients on methadone or buprenorphine require a different approach. For patients who present on these medications, involvement of anesthesia, pain, or addiction specialists beginning in the preoperative period is recommended where available. Daily doses of methadone should be continued with the addition of short-acting opioids and multimodal agents to manage the acute pain, while also considering the possibility of cross-tolerance.[42] Cross-tolerance may explain why patients on maintenance opioids often require higher and more frequent dosing of opioid analgesics. Analgesic dosing should be continuous to prevent reemergence of pain and reduce patient suffering and anxiety regarding adequate pain control. Mixed agonist/antagonist opioids should

be avoided.[42] Buprenorphine, with its high affinity to the μ receptor, requires slightly more consideration with acute pain management. Options can include continuing maintenance therapy with titration of a short-acting opioid, dividing the dose of buprenorphine with administration every 6 to 8 hours, discontinuing buprenorphine, and treating the patient will full opioid agonist analgesics with titration to avoid withdrawal, or converting to methadone at 30 to 40 mg/d.[42] After treatment of acute pain, it should be kept in mind that a buprenorphine restart can precipitate opioid withdrawal.[42]

Pain Control in Presence of Substance Use Disorder

Substance use disorder is a common problem; it is a complex condition characterized by compulsion and preoccupation with a substance despite negative consequences. Patients with substance use disorder, like opioid-tolerant patients, may be at risk of having their acute pain undertreated related to their preexisting opioid tolerance, fears of precipitating respiratory depression and fears of triggering relapse.[43]

Providers may also fear inducing relapse. Patients with inadequate pain control, however, are more likely to self-medicate.[43] Providers should avoid using less potent opioids for this reason. The use of objective findings and specific pain complaints should provide the clinician with reassurance that the patient is not drug-seeking, which is a common prejudgment. Drug abuse screening tools and multimodal anesthesia should be used, but more research is needed to improve treatments for optimal pain relief and to prevent central sensitization, chronic pain, and impaired physical and social functioning in this patient population.[43]

Pain Control for Patients near the End of Life

The patient with cancer may be faced with significant pain at the end of life from a variety of causes, including tumor burden, surgical procedures, or other components of total pain. Barriers to pain control at the end of life include patient factors, clinician factors, family factors, and system factors. Patient factors may include the misconception of a dichotomous choice of being awake and in pain versus having pain controlled and being sedated, may fear the stigma of addiction, and might want to avoid opioid-related side effects. Clinicians may fear the inability to adequately recognize pain, may fear hastening death (although protected by the doctrine of double effect) and must deal with the competing goals of providing cure versus comfort. Family factors include desire for the patient to be alert and the fear of hastening death. System factors include fragmented care and medicolegal concerns regarding opioid prescribing.[44]

Three aspects of “a good death” have been previously described and include the following: avoidance of distress and suffering, alliance with patient’s preferences and wishes, and consistence with clinical and cultural standards.[45] Pain control and patient comfort should be achieved at the end of life, with involvement of palliative care clinicians when beyond the scope of the surgeon.

NONPHARMACOLOGIC STRATEGIES

Nonpharmacologic strategies can be key elements in multimodal pain control. Although the data are limited, this section provides a brief review of some nonpharmacologic modalities used in the general postoperative setting, as well as in the management of chronic cancer pain.

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) is a form of psychotherapy that has been shown to relieve distress and pain in various cancer populations.[46] Hypnosis, a commonly used

CBT technique, has also been evaluated in the acute postsurgical setting. A meta-analysis indicated that hypnosis treatment groups had better outcomes than 89% of patients in control groups. In this nonpharmacologic intervention, a hypnotist guides a patient through peaceful and relaxing imagery in the induction phase to allow the patient to feel more relaxed, less distracted, and more open to therapeutic suggestions. In the application phase, the hypnotist makes suggestions for the patient to change sensorial or cognitive processes, physiology, or behavior. Hypnosis as an adjunct to postoperative pain control may be a powerful tool in addressing symptoms after surgery.[47]

Acupuncture

Acupuncture originated in Chinese medicine and involves the insertion of needles to defined depths, followed by manipulation with forces, heat, or electrical stimuli. A systematic review and meta-analysis found that patients treated with acupuncture or related techniques had less pain and used less opioid analgesics on the first day after surgery compared with controls.[48] Few randomized controlled trials have been conducted to evaluate acupuncture for cancer-related pain but contained small sample sizes, heterogeneous cancer diagnoses, and differing study methodologies. No definitive conclusion has been made to recommend acupuncture as part of standard care for treating cancer pain, but can continue to be used for postsurgical pain.[49]

Exercise

Prehabilitation training is the process of optimizing physical functionality before surgery and can include a combination of aerobic exercises, strength training, and functional task training.[50] A systematic review evaluated its utility in function, pain, and quality of life following surgery. They concluded that there was no benefit to pain, quality of life, readmissions or nursing home placement, but there was a significant reduction in the need for postoperative rehabilitation.[50]

Mishra and colleagues[51] conducted a Cochrane review containing 40 trials testing exercise interventions on quality of life for cancer survivors. Their results suggested that exercise compared with control has a positive impact on global health-related quality of life, body image/self-esteem, emotional well-being, sexuality, sleep disturbance, and social functioning. They also found that exercise interventions decreased anxiety, fatigue, and pain at 12 weeks' follow-up. They do mention that all trials reviewed were at high risk for performance bias and results should be interpreted cautiously.[51] Given the impact of total pain on the patient with cancer, exercise should still be considered as a nonpharmacologic option to control pain long after surgery. Additional research with focus on exercise and its impact specifically on cancer and postsurgical pain is needed.

DISCUSSION AND FUTURE DIRECTIONS

Pain is highly prevalent in the population of patients with cancer and spans from diagnosis through survivorship. Given the complexity of cancer pain, a multimodal approach is essential in managing perioperative pain. Chronic postsurgical pain continues to increase as survival outcomes improve, and the concept of total pain underscores the importance of managing more than just physical pain. Pain management begins in the preoperative setting, with the focus on patient education and expectation setting. Intraoperatively, anesthesia plays an important role in helping reduce postoperative nausea and vomiting, length of stay, and pain intensity. Management of postoperative pain should focus on how the pain is impacting the patient's function and

recovery and may include both pharmacologic and nonpharmacologic therapies. Future directions will involve a multidisciplinary approach and likely include the surgeon, pain specialists, and behavioral therapists. More research needs to be done to assess the true efficacies of many of the pharmacologic modalities. The responsibility of the surgeon is to assess all dimensions of their patients' pain so that the appropriate treatment may be sought.

CLINICS CARE POINTS

- Pain impacts a large proportion of the population of patients with cancer, averaging 53% across the cancer continuum, at any given point from diagnosis to survival.
- Cancer pain is characterized by multimorphism and "total pain" must be considered.
- The focus of preoperative discussion should be education and expectation setting.
- Anesthesia plays an important role in maintaining homeostasis and reducing the stress response intraoperatively.
- Opioids are a cornerstone of postoperative pain therapy, but risk of prolonged use is a concern in the population of patients with cancer.
- Postoperatively, multimodal therapy is important in reducing postoperative opioid consumption, but further research needs to be done to evaluate the optimal means of opioid discontinuation while still decreasing postoperative pain.

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