Chapter 13

SPECIAL FEATURES OF POSTOPERATIVE PAIN MANAGEMENT IN THE ONCOLOGICAL PATIENT

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ABSTRACT

Millions of cancer patients are diagnosed each year. Many of these patients require surgical procedures that can cause postoperative pain. Poor postoperative pain control is associated with persistent chronic pain, poor patient satisfaction, increased healthcare costs and psychological consequences. Postoperative pain remains one of the most common challenges following inpatient and outpatient surgery. Oncology patients often present with acute or chronic pain prior to surgery, opioid tolerance or contraindications to some analgesics, making postoperative pain management difficult. In this chapter, we will review some aspects to consider in the management of postoperative pain in the oncological patient.

Keywords: Cancer, postoperative pain, oncology

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INTRODUCTION

In 2020, an estimated 19.3 million patients were diagnosed with cancer worldwide [1]. Many of them needed or will need surgery to diagnose, treat, or palliate their disease [2]. These numbers indicate that a large number of patients might have suffered or will suffer from significant acute postoperative pain. Postoperative pain is defined by the ASA (American Society of Anesthesiologists) as pain that is present in the patient due to the disease, the surgical procedure and its complications, or a combination of both, and is primarily characterized as acute, time-limited, predictable and avoidable.Postoperative pain can be aggravated by factors such as patient expectations, treatment-related complications, extensive incisions or extensive surgical trauma, medication shortages, drug allergies, chronic pain and tolerance to analgesics such as opioids [3,4]. The site, nature and duration of surgery are factors that influence the occurrence of postoperative pain. The type and extent of the surgical incision is another important factor. Incisions in areas of tension or in anatomical folds are more painful. Poorly managed acute postoperative pain is associated with poor clinical outcomes, poor patient satisfaction, prolonged hospitalization, increased healthcare costs, delayed wound healing, psychological stress and chronic pain [4].

There are basically two types of surgical procedures: minimally invasive surgery and open surgery. The current trend is to perform surgery using a minimally invasive procedure, reducing possible side effects and hospital stay. In many cases, we will not be able to define whether the pain was caused by the disease itself or by the surgery. The types of surgery with the highest incidence of pain after surgery are: amputations (50-80%), thoracotomies (5-65%) and breast surgery (20-50%) [5].

In the present review, we will summarise specific aspects related to the management of acute postoperative pain in cancer patients. And we will also provide evidence on how poorly managed acute pain in cancer patients may affect the development of persistent pain and opioid use.

PARTICULARITIES OF PHARMACOLOGICAL MANAGEMENT

The management of acute postoperative pain in cancer patients is complicated. Cancer patients may present with acute and chronic pain syndromes prior to surgery [6]. Pain syndromes prior to surgery may be due to pathological fractures, tumour progression, acute or chronic toxicity from chemoradiotherapy or osteonecrosis [4]. This complicates their management, as they may be refractory to analgesics or complicate basics such as positioning on the operating table or in hospital beds [4]. Many cancer patients may have neuropathic pain secondary to tumour invasion of nerves and plexuses or neuropathies secondary to radiotherapy or chemotherapy treatment [7]. Neuropathies worsen postoperative pain and often do not respond to traditional analgesics.

Effective treatment of pain with a single drug/therapy is difficult to achieve without a large expenditure of equipment and human resources and/or side effects. For this reason, the simultaneous use of more than one class of analgesic drug or technique is recommended, in order to improve analgesia through additive or synergistic effects while reducing opioid-induced side effects [8]. The aim of the combination is to use lower doses of each of the drugs while maintaining effective analgesia and at the same time being able to reduce side effects [9, 10]. The concept of multimodal analgesia for postoperative pain management was introduced by Kehlet and Dahl in 1993 [11]. For more than 20 years, the various postoperative pain management guidelines have identified the use of multimodal analgesia as an essential part of their guidelines. Recently, the joint guidelines of the American Pain Society, American Society of Regional Anesthesia and Pain Medicine, and American Society of Anesthesiologists recommend the combination of analgesics and techniques as well as non-pharmacological measures with a high degree of evidence [12]. However, the application of these techniques in routine clinical practice is apparently a challenge. Some of the drugs available in multimodal analgesia are paracetamol, non-steroidal anti-inflammatory drugs, local anaesthetics,

gabapentinoids, ketamine and glucocorticoids. However, despite growing awareness of the value of multimodal pain management plans, opioid monotherapy remains the mainstay of postoperative pain management.

The following is an overview of the therapeutic arsenal available for pain management in cancer patients and its peculiarities.

Regional Analgesia

In recent years, there has been an increase in the use of regional techniques for surgery and perioperative pain management. Regional analgesia is an effective strategy to treat acute postoperative pain and a key component of multimodal analgesia. Regional analgesia has opioid- and general-anesthetic sparing effects and modulates the inflammatory and immune response to surgery [13]. These effects have led investigators to hypothesize that the use of regional anesthesia could have a significant beneficial impact on the survival of patients with cancer by reducing the risk of cancer recurrence [4]. A Cochrane review published in 2014 assessed the influence of anaesthetic technique on the risk of tumour recurrence and concluded that patients receiving regional anaesthetic techniques had longer overall survival and longer time to tumour progression. The data were not of very good quality and the results could be biased by concurrent therapies received by the patients [14, 15]. Furthermore, a recent consensus of the American and European Society of Regional Anaesthesia concluded that there is no strong evidence to suggest regional analgesia reduces cancer recurrence [16].

There are cancer patients who are not candidates for regional anaesthesia due to preference, misinformation, febrile neutropenia, thrombocytopenia or need for anticoagulation. In those patients who are not candidates for regional anaesthesia, the administration of systemic non-opioid analgesics (intravenous lidocaine, paracetamol, ketamine or non-steroidal anti-inflammatory drugs) together with judicious administration of opioids play an important role in the management of their postoperative pain [4].

Non-Opioid Drugs

Paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), dexmedetomidine, intravenous lidocaine, pregabalin and gabapentin are drugs that are recommended to relieve acute postoperative pain and reduce the use of opioids in the context of multimodal analgesia after surgery in oncology patients [17, 18]. However, not all cancer patients are candidates for these analgesics due to their potential side effects, such as impaired renal function, risk of gastrointestinal bleeding, elevated blood pressure, risk of fractures, etc.

We have to consider that some cancer patients may suffer cognitive impairment secondary to chemotherapy or radiotherapy. This cognitive impairment may be aggravated after surgery. Therefore, in the pre-surgical planning of the drugs we may use, we have to take into account that some drugs, such as gabapentinoids or ketamine, may cause excessive sedation and dizziness. In contrast, intravenous lidocaine seems to cause less sedation and dizziness.

Some studies have linked the use of non-opioid analgesics to better cancer outcomes. NSAIDs may influence cancer recurrence due to their effects on COX-2 and PGE 2, which are the main mediators of cancer progression. COX-2 inhibition may have a direct effect on cancer cell proliferation [19]. Aspirin has been associated with reduced colorectal cancer-specific mortality [20]. Despite this, we must consider that chronic use of non-steroidal anti-inflammatory drugs is limited by their side effects. This area is still under investigation.

Opioids

Opioids are the most commonly used drugs to relieve postoperative pain in cancer patients. Nevertheless, the main scientific societies recommend reducing their perioperative prescription due to their side effects and the opioid epidemic in USA.

The evidence on the use of opioids and their effect on cancer cell proliferation is limited and contradictory [21].

ACUTE PAIN MANAGEMENT IN THE OPIOID-TOLERANT PATIENT

An important issue in relation to the postoperative pain management of cancer patients is the fact that many of them will be on long-term and often high-dose opioids and will therefore have to be considered opioid tolerant. Tolerant states are characterised by a shorter duration and decreased intensity of analgesia, euphoria, sedation and other central nervous system effects caused by opioids. This is a predictable pharmacological adaptation. Chronic opioid exposure results in a rightward shift of the dose-response curve, with increasingly higher doses required to maintain the same effects. Patients who are chronic opioid users should be identified preoperatively and informed of the potential risk of pain aggravation and their increased postoperative opioid requirements, as well as other analgesic techniques that may complement them [22, 23]. For situations where regional techniques are used (mainly epidurals), even if we administer opioids by this route, this is not sufficient and we must provide at least half of the preoperative requirements of morphine by the systemic route. Non-opioid analgesic adjuvants should be used to reduce opioid requirements and provide a multimodal approach to analgesia. These may include selective or non-selective NSAIDs, paracetamol and ketamine.

After surgery, the switch from intravenous or epidural infusion to oral infusion or to the formulation the patient was previously taking requires special attention in chronic opioid users. These patients require longer analgesic methods compared to others who have not previously received opioids [22, 23]. In patients who cannot tolerate oral intake postoperatively, parenteral substitution at equi-analgesic doses is required.

PERSISTENT POSTOPERATIVE PAIN IN CANCER PATIENTS

A definition of chronic or persistent postoperative pain defended by Macrae [24] and later redefined by Werner [25], is pain that occurs after a surgical procedure lasting at least 3 months, excluding other possible causes (cancer, chronic infection...) and it`s located in the surgical field or a referred area (Figure 1).

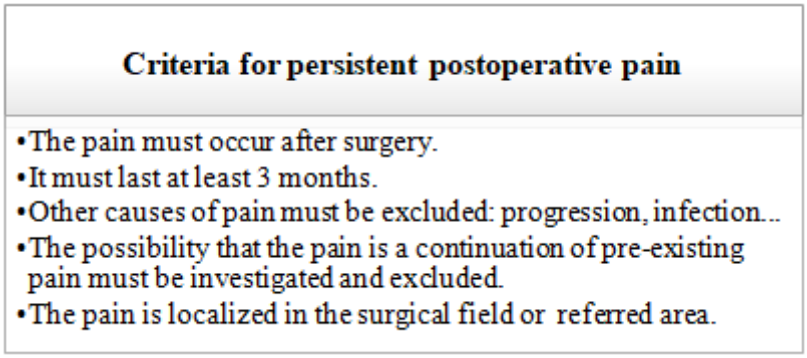

Figure 1. Criteria for chronic or persistent postoperative pain. [24, 25]

The factors most related to the possibility of developing persistent postoperative pain are: preoperative pain, psychosocial and emotional aspects, poor postoperative pain control and nerve damage during surgery (Figure 2). Incidence varies widely between series, possibly related to problems in diagnosis. The surgeries most at risk of developing chronic postoperative pain are amputation, mastectomy and thoracotomy. The aetiopathogenesis of persistent postoperative pain is unknown, it is postulated that peripheral nerve damage and subsequent changes in neuronal plasticity both peripherally and centrally may trigger persistent pain in certain patients. The factors associated with an increased risk of persistent postoperative pain are derived from the surgical intervention itself and the characteristics of the patient [26]. Suggested ways to minimise the risk of persistent postoperative pain are aimed at avoiding or blocking the factors that are related to its occurrence. Surgeons can play

an important role in reducing persistent postoperative pain by using minimally invasive and nerve-sparing techniques, such as sentinel node biopsy for mastectomy, thus avoiding axillary dissection and intercostal nerve damage. In addition to addressing surgical factors, we must address the emotional aspects of the patient and provide multimodal analgesia, including where possible the use of regional analgesia.

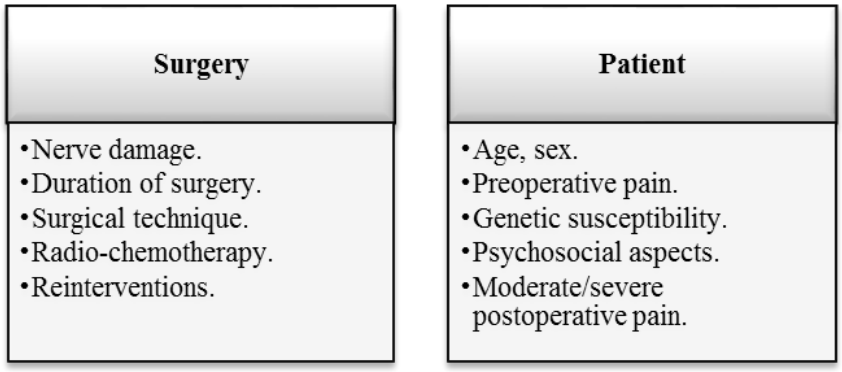

Figure 2. Factors related to the development of persistent postoperative pain.

Some drugs used to prevent persistent postoperative pain as analgesic adjuvants include gabapentin, pregabalin and ketamine. Gabapentin and pregabalin improve postoperative pain control and also protect against the development of persistent postoperative pain. Ketamine is commonly used for the treatment of acute pain in the perioperative setting. Ketamine in opioid-dependent patients is known to prevent opioid-induced hyperalgesia. It is a drug that is part of multimodal analgesia protocols. However, the literature in this area is limited and there is no solid evidence on the role of any intervention to prevent or treat this complex entity.

There are few prospective studies evaluating persistent postoperative pain in the cancer patient. The most widely published in the literature on persistent postoperative pain is chronic pain after breast cancer surgery. Persistent post-mastectomy pain is increasingly recognized [27,28]. Persistent postoperative pain affects 20-50% of mastectomised women. Risk factors associated with increased risk of persistent postmastectomy

pain are younger age, previous preoperative pain, axillary lymph node dissection, adjuvant radiotherapy, acute postoperative pain and psychosocial factors [28]. It appears that sentinel lymph node biopsy is a protective factor for persistent postoperative pain after mastectomy [28]. According to the literature, physical therapy [29], psychological [30] and pharmacological [31] care may help to mitigate persistent postmastectomy pain.

CONCLUSION

The management of acute postoperative pain in cancer patients can be complicated. Postoperative pain relief requires multimodal analgesia, with regional analgesia sometimes being a key technique. Opioids are the most commonly used drugs for postoperative pain relief in cancer patients. Opioid tolerance in cancer patients must be taken into account to avoid poor pain relief.

Most of the published literature on persistent postoperative pain in cancer patients focuses on patients with breast cancer surgery. As with other types of malignancies, this pain is complicated by factors such as radiochemotherapy toxicities, among other factors. Adequate postoperative analgesia would help reduce the risk of persistent postoperative pain.

REFERENCES

[1] International Agency for Research on Cancer. *Cancer Incidence in Five Continents.* IARC, WHO. [Internet] [Last accesed: October 2021]. Available from: https://ci5.iarc.fr/Default.aspx.

[2] Meara JG, Leather AJ, Hagander L, Alkire BC, Alonso N, Ameh EA, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. *Lancet.* 2015; 386(9993): 569-624.

[3] Hsia IK, Dexter F, Logvinov I, Tankosic N, Ramakrishna H, Brull SJ. Survey of the national drugs shortage effect on anesthesia and patient safety. *Anesth Analg.* 2015;121 (2): 502-6.

[4] Cata JP, Corrales G, Speer B, Owusu-Agyemang P. Postoperative acute pain challenges in patients with cancer. *Best Pract. Res Clin Anaesthesiol.* 2019; 33(3): 361-71.

[5] Ip HY, Abrishami A, Peng PW, Wong J,Chung F. Predictors of postoperative pain and analgesic consumption: A qualitative systematic review. *Anesthesiology*. 2009; 111 (3): 657–77.

[6] BuchakjianMR, Davis AB, Sciegienka SJ, Pagedar NA, Sperry SM. Longitudinal perioperative pain assessment in head and neck cancer surgery. *Ann Otol Rhinol Laryngol*. 2017; 126(9): 646-53.

[7] Seretny M,Currie GL,Sena ES,Ramnarine S,Grant R,MacLeod MR, et al. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Pain*. 2014; 155(12):2461-2470.

[8] Dalh JB, Rosenberg J,Dirkes WE,Mogensen T,Kehlet H. Prevention of postoperative pain by balanced analgesia. *Br J Anaesth.* 1990; 64(4):518-20.

[9] Ong CK, Seymour RA,Lirk P, Merry AF.Combining paracetamol (acetaminophen) with nonsteroidal anti-inflammatory drugs: A qualitative systematic review of analgesic efficacy for acute postoperative pain. *Anesth Analg.* 2010; 110(4):1170-79.

[10] Solomon RE, Gebhart GF. Synergistic anti-nociceptive interactions among drugs administered to the spinal cord. *Anesth Analg.*1994; 78(6):1164-72.

[11] Kehlet H, Dahl JB. The value of "multimodal" or "balanced" analgesia in postoperative pain treatment. *Anesth Analg*. 1993; 77(5): 1048-56.

[12] Chou R, GordonDB,de Leon-Casasola OA, RosenbergJM,Bickler S,Brennan T, et al. Guidelines on the Management of Postoperative Pain Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of RegionalAnesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain*. 2016; 17(2):131-57.

[13] Vicente D,Patino M, Marcus R, Lillmoe H,Limani P, Newhook T, et al. Impact of epidural analgesia on the systemic biomarker response after hepatic resection. *Oncotarget*. 2019; 10 (5); 584-594.

[14] Cakmakkaya OS,Kolodzie K,Apfel CC,Leon Pace N. Anaesthetic techniques for risk of malignant tumour recurrence. *Cochrane Database Syst Rev*. 2014; 7;(11).

[15] Tornero C, Fernández LE, Orduña J. Multimodal analgesia and regional anaesthesia. *Rev Esp Anestesiol Reanim*. 2017; 64(7): 401-405.

[16] Missair A, Cata JP,Votta-Velis G,JohnsonM,Borgeat A,Tiouririne M,et al. Impact of perioperative pain management on cancer recurrence: an ASRA/ESRA specialarticle. *Reg Anesth Pain Med*. 2019; 44(1): 13-28.

[17] Nelson G, Bakkum-Gamez J, Kalogera E, Glaser G, Altman A, Meyer L, et al. Guidelines for perioperative care in gynecologic / oncology: enhanced Recovery after Surgery (ERAS) Society recommendations - 2019 update. *Int J Gynecol Cancer*. 2019; 29(4): 651-668.

[18] Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for perioperative care in elective

colorectal surgery: enhanced recovery after surgery (ERAS) society recommendations: 2018. *World J Surg*. 2019; 43(3): 659-95.

[19] Karnezis T, Shayan R, Caesar C, Roufail S, Harris NC, Ardipradja K, et al. VEGF-D promotes tumour metastasis by regulating prostaglandins produced by the collecting lymphatic endothelium. *Cancer Cell*. 2012; 21(2):181-195.

[20] McCowan C, Munro AJ, Donnan PT, Steele RJ. Use of aspirin post-diagnosis in a cohort of patients with colorectal cancer and itsassociation with all-cause and colorectal cancer specific mortality. *Eur J Cancer*. 2013; 49(5):1049-1057.

[21] Simon AA, Buggy DJ. Does regional anesthesia and analgesia oropioid analgesia influence recurrence after primary cancer surgery? Anupdate of available evidencia. *Best Pract Res Clin Anaesthesiol*. 2013; 27(4): 441-56.

[22] Schug SA. Acute pain management in the opioid-tolerant patient. *Pain Manag.*2012; 2(6): 581-91.

[23] Huxtable CA, Roberts LJ, Somogyi AA, MacIntyre PE. Acute pain management in opioid-tolerant patients: a growingchallenge. *Anaesth Intensive Care*. 2011:39(5): 804-23.

[24] Macrae WA. Chronic post-surgical pain: 10 years on. *Br J Anaesth*. 2008; 101(1): 77 - 86.

[25] Werner MU, Kongsgaard UE. I. Defining persistent post-surgical pain: is an update required? Br J Anaesth.2014; 113:1– 4.

[26] Niraj G, Rowbotham DJ. Persistent postoperative pain: where are we now? *Br J Anaesth*. 2011; 107(1): 25-9.

[27] Tait RC, Zoberi K, Ferguson M, Levenhagen K, Luebbert RA, Rowland K, et al. Persistent post-mastectomy pain: risk factor and current approaches to treatment. *J Pain*.2018; 19(12): 1367-1383.

[28] Brackstone M. A review of the literatura and discussion: establishing a consensusfordefinition of post-mastectomy pain syndrome to provide a standarizedclinical and researchapproach. *Can J Surg*. 2016; 59(5): 294-5.

[29] Cheville A, Tchou J. Barriers to rehabilitation following surgery for primary breast cancer.*J Surg Oncol*. 2007; 95 (5): 409–418.

[30] Jassim GA, Whitford DL, Hickey A, Carter B. Psychological interventions for women with non-metastatic breast cancer. *Cochrane Database Syst Rev*. 2015; 28(5).

[31] Paice JA, Portenoy R, Lacchetti C, Campbell T, Cheville A, Citron M, et al. Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline.*Clin Oncol*. 2016; 34 (27): 3325–45.