REVIEW ARTICLE

Perioperative Pain Management in Gynecologic Oncology Surgery

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Abstract  Postoperative pain is a normal reaction to surgical intervention; however, it has been shown to increase morbidity, thus compromising the quality of recovery, which entails a delay in hospital discharge, increased risk of wound infection, and respiratory or cardiovascular complications, with an increase in mortality. Pain syndromes observed in patients with gynecologic oncology pathology result from three primary etiologies: those directly occurring due to the tumor, those deriving from treatments focused on reducing the tumor and those syndromes that are entirely independent of cancer or its treatment. Postoperative pain optimal management requires understanding the pathophysiology of pain and knowing the methods to be able to assess it in each patient, as well as knowledge on the different options available to control it. The key points that have to be considered are: the type of patient, type of surgical procedure, skills of the surgeon and anesthesiologist, and support of the working team. Improving the treatment of postoperative pain requires a broader perspective, since most healthcare providers have been shown to focus only on the postoperative period; however, ideal management is that where interventions are carried out before, during, and after surgery. (creativecommons.org/licenses/by-nc-nd/4.0/).

KEYWORDS
Acute pain; Postoperative pain; Gynecologic surgery; Oncologic Surgery; Multimodal analgesia

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INTRODUCTION

Pain is the most serious and feared symptom in cancer patients. Data yielded by 52 reviewed articles showed that pain is rather common, with figures of 33% in cancer patients, 59% in patients on cancer treatment, and 64% in patients with metastasis or at advanced stages of the disease being reached. More than one-third of patients with pain in this review classified their pain as being moderate-to-severe. The consequences of pain poor control are devastating and can include dysfunction, social isolation, and emotional and spiritual stress, as well as discontinuation of potentially curative treatment, with this having an impact on disease recurrence-free periods and patient survival.

ACUTE PAIN

Pain syndromes commonly associated with the cancer patient result from three primary etiologies: the first one is associated with the pain experienced by direct relationship with disease progression; the second results from the different treatment schemes, progression control, and debulking focused on controlling the disease and reducing its impact and including oncologic surgery procedures, neoadjuvant and adjuvant chemotherapy, radiotherapy, intraoperative anesthesia, radiotherapy and hormone therapy. Finally, there is the pain that occurs entirely independently of the neoplastic disease process and/or its treatment.

Acute pain is considered to be an immediate sensorial consequence of nociceptive system activation, an alarm signal triggered by the body’s protecting systems. Acute pain is generally caused by somatic or visceral tissue damage, and it develops with a time course closely following the repair and healing of the causative lesion. If there are no complications, acute pain disappears with the lesion that caused it.

The International Association for the Study of Pain (IASP), in Kopf and Batel’s revision, defines acute pain as recent-onset and limited-duration pain, and its treatment should be aimed at having a protective role and preventing peripheral nervous system excitation and damaged tissue hypersensitivity, with the purpose of avoiding the presence of chronic pain syndromes that were initially acute.

POSTOPERATIVE ACUTE PAIN

Postoperative acute pain is defined as secondary to a direct or indirect aggression produced during a surgical act, taking into consideration pain caused by the surgical technique, anesthetic technique, inadequate posture, muscle contraction, and bladder or intestinal distension. Its importance lies in its elevated frequency, its inadequate treatment, and its consequences on patient recovery and survival. Formerly it was regarded as a normal response to surgical intervention; however, the direct consequences of undertreatment have been currently defined, which results in direct repercussions on sympathetic activity with increased oxygen consumption, myocardial and tissue ischemia, fear, anxiety, pulmonary complications, decreased immune response, and more recently, presence of surgical procedure-related chronic pain syndromes or chronic postoperative pain.

Pain enduring more than one month after surgery and persisting for at least three months with additional neuropathic symptoms occurs in 10–50% of common procedures, and 2–10% of these patients will continue with chronic pain. Pain that is not adequately treated tends to reduce patient satisfaction and impact on morbidity and mortality. Acute pain that becomes untreatable and persistent is known as chronic postoperative pain, which can have a significant impact on patient quality of life and daily activities, including sleeping and mood disorders.

PERIOPERATIVE MANAGEMENT

Patients will be concerned about perioperative pain control, and preoperative assessment is therefore an important opportunity to discuss the plan to be used, as well as to explain what to expect of pain control, which never should be that “the patient will experience no pain”. In this assessment, cognitive and psychological aspects that play a significant role in postsurgical pain severity can be identified. There is evidence that factors such as anxiety, depression, and catastrophism are essential pieces in the perception of pain and in coping with the experience of pain. Once the management plan has been established, the medical team and nursing staff should be in close communication in order to identify and report possible adverse effects.

Preemptive analgesia is a method intended to prevent or attenuate central sensitization resulting from the painful stimulus and the inflammatory reaction developing following the lesion. The efficacy of this modality (epidural analgesia, local anesthetic infiltration into the wound, use of non-steroidal anti-inflammatory drugs [NSAID], ketamine, clonidine) has shown beneficial effects in postoperative pain control.

Pain associated with abdominal surgical procedures is multi-factorial and includes parietal components originating from the surgical site, and visceral components originating from intra-abdominal structures.

In those patients who will undergo abdominal procedures, the use of transversus abdominis plane (TAP) block should be considered, which is not necessary in laparoscopic procedures, since pain in these cases is mainly on port insertion sites, where local anesthetic wound infiltration has shown benefits.

These effects were demonstrated by Lowenstein, et al, when they carried out a randomized trial with placebo and lidocaine 1% infiltrated into the incision site prior to the surgical procedure (hysterectomy), where the outcome was a significant reduction of postoperative pain within the first few hours.

TRANSOPERATIVE MANAGEMENT

The response to surgical stress is characterized by neuroendocrine, metabolic and inflammatory changes, which
adversely affect patient recovery. With recent advances in anesthetic and surgical techniques, this degree of surgical stimulation has decreased. Anesthetic depth, multimodal approaches, and surgical invasion reduction have been shown to result in postoperative pain decrease.4

Surgical technique

Minimally invasive surgery is currently accepted as an integral part of gynecologic oncology surgery, which has prompted the performance of more advanced procedures in oncologic surgeries, showing promising results with robotic surgery incorporation in comparison with conventional techniques.7 The use of minimally invasive surgery in gynecologic oncology surgery has increased since 2006, when randomized trials showed it is a feasible and safe technique, with results including a decrease in hospitalization days and less postoperative pain.18

Anesthetic technique

Multiple studies on general surgery have shown that intraperitoneal local anesthetic administration can reduce postoperative pain and the need for postoperative opioids.19 The same results have been observed in gynecologic procedures for benign pathologies such as tubal ligation, cystectomy or endometriosis surgery.20 A study conducted by Rivard, et al. demonstrates pain control superiority after intraperitoneal administration of bupivacaine in hysterectomy and cancer staging surgery.21 Since some decades ago, multiple studies have been carried out comparing the anesthetic technique used during surgery to assess its effect on postoperative pain control. The anesthetic technique has been shown to impact on postoperative pain evolution and control.22

The use of anesthesia and subsequent epidural analgesia has shown pain improvement in comparison with other techniques such as patient controlled analgesia (PCA), and has therefore been accepted by numerous gynecologic oncology groups.23 There are meta-analyses supporting the use of epidural analgesia, since it shows superiority especially in those patients who underwent laparotomy or thoracotomy.24

Catro, et al. demonstrated that those patients who underwent hysterectomy and were anesthetized with neuroaxial technique, specifically with spinal anesthesia, showed a significant improvement in the quality of recovery, and lower levels of pain reported during the first 48 hours after surgery, with less side effects.25 If we add the results of Collins, et al. to this technique by adding intrathecal opioid together with local anesthetic, postoperative pain is further reduced.26

Recent reports suggest the use of neuroaxial techniques plus addition of regional blocks (TAP, peripheral nerve block, nervuous plexuses block) in order to provide effective analgesia and being able to reduce opioid systemic effects;27 however, the results obtained by Siddiqui, et al. show that postoperative opioid decrease occurs only in the first 24 hours.

With the spinal and epidural techniques, a neuroaxial block of the nociceptive stimulus occurs. When using epidural anesthesia is decided, local anesthetic and opioid administration is recommended to be performed prior to the incision and to continue postoperatively; in addition to providing excellent analgesia, this has been also shown to facilitate mobilization and postoperative physical therapy, as well as lower incidence of postoperative ileus.28

De León-Casasola, et al. demonstrated that in those patients undergoing cancer-related hysterectomy, intestinal function recovery was faster in those receiving patient-controlled epidural analgesia (PCEA) than in those who received PCA.29 In the study by Rivard, et al. in all patients who underwent laparotomy with vertical abdominal incision with suspected gynecologic malignancy, PCEA was shown to be associated with a decrease in pain scale levels and postoperative opioid total use, with postoperative ileum occurring in 13.4% of patients.30,29 According to meta-analyses results, epidural analgesia provides superior postoperative pain control in comparison with systemic opioid administration, in addition to an important decrease in adverse effects.30,31

Surgical wound infiltration with local anesthetics has a rapid onset of action, and with vasoconstrictor addition the effect can be prolonged. The selection of the anesthetic to be used depends on the extension of the area that is wanted to be covered and the desired effect duration. Many studies have assessed the use of liposomal bupivacaine, demonstrating that its effect lasts up to 72 hours postoperatively.32

Intravenous drugs

The use of intravenous lidocaine in up to 100 mg boluses and subsequent continuous administration at 2-3 mg/hour has been shown to have analgesic effects and anti-inflammatory properties, as well as to reduce opioid requirements.3

Beta-blockers have been used to minimize sympathetic responses both at the moment of endotracheal intubation and induced by the surgical stimulus, which decreases inhaled analgesics and opioid requirements.3

Alpha-2 agonists such as clonidine and dexmedetomidine have analgesic properties and have been shown to reduce postoperative pain and opioid consumption, with this effect being superior with dexmedetomidine; however, it cannot be used in all patients, especially in those with heart blocks or ventricular dysfunction, owing to the cardiovascular changes it produces.3

POSTOPERATIVE MANAGEMENT

Intraoperative management is usually addressed by anesthesiologists, whereas postoperative pain is traditionally managed by surgeons, although this tendency is changing into a common perioperative management by the anesthetic-surgical team.3

Since the PCA system introduction in the 1980s, postoperative pain daily management has extensively been optimized.4 This PCA provides adequate pain control, great satisfaction, and less adverse effects compared with administration on an as-needed basis. When patients experience pain, they self-administer the medication and, once the pain is reduced, they stop self-administering the medication. The initial dose is that which is required to reduce pain to 4/10 in the numeric rating scale (NRS), or to a respiratory rate of 12 breaths/minute or less, after which, the PCA pump is programmed establishing the bolus doses, maximum number of boluses in one hour and the closure interval, which limits how close consecutive doses can be. PCA is usually used
with morphine or hydromorphone; fentanyl is not recommended unless the patient is under continuous monitoring as, for example, in the ICU. There are different routes of administration, including transdermal, epidural, in peripheral nerves, and the most widely studied is the intravenous route. Numerous studies have demonstrated epidural PCA superiority in comparison with intravenous administration. Postoperative beneficial effect is more significant in high-risk patients or in those who undergo major procedures. Peripheral nerve PCA results in increased postoperative analgesia and satisfaction, especially in limb surgery. In the study by Rivar, et al., the use of TAP with PCA was shown to reduce opioid medication, but only within the first 24 hours post-surgery, without difference in pain control in the ensuing days, which is consistent with previous studies in gynecologic oncologic surgery that also concluded that the PCEA approach should be the method of choice in patients undergoing gynecologic oncology surgery with abdominal approach and vertical incision.

**Opioids**

To ensure opioid adequate use in postoperative pain management, education of both medical staff and patients is required. Opioids remain the mainstay in the control of postoperative pain; however, they have been associated with side effects such as nausea, vomiting, dizziness and constipation. They offer the convenience of different routes of administration, including intravenous, intramuscular, oral, transdermal or transmucosal, and provide fast and effective analgesia in patients with moderate-to-severe pain.

Morphine is the prototype of these drugs; it has a slow onset of action and intermediate action duration of approximately five hours, with a two-hour half-life. Its metabolites are excreted by the kidney, and its adverse effects are therefore prolonged in patients with renal failure.

Hydromorphone is a semi-synthetic opioid that is four to six-fold more potent than morphine; its onset of action is faster, but action duration is shorter; it has lower incidence of itching and sedation than morphine.

Fentanyl is a semi-synthetic opioid that is 50 to 80-fold more potent than morphine. It has a fast onset of action of 5-7 minutes, with a short duration of action of approximately one hour. In case immediate analgesia is required, the IV route is preferred. Although there are fentanyl-releasing patches, their use is not recommended for the management of immediate postoperative pain because changes in drug release vary with the patient body temperature, the required time to reach ideal plasma concentrations is very slow, and no quick dose adjustments can be made.

Oxycodone is a potent opioid agonist that is metabolized by the liver. It is more effective than morphine in the management of visceral pain.

Tramadol is an effective analgesic in mild-to-moderate pain and for neuropathic pain owing to its mechanism of action as a mu-agonist and serotonin and noradrenalin re-uptake inhibitor. The risk of respiratory depression is lower compared with other opioids.

Buprenorphine is an opioid receptor partial agonist, and has an analgesia ceiling effect in animal models, as well as in humans for respiratory depression. It is a safe drug in patients with renal failure, which makes it an attractive option for postoperative pain management in comparison with other opioids.

### Non-opioid analgesics

Paracetamol is a medication that can be an effective component in multimodal analgesia. It can be administered orally, rectally, and parenterally. It significantly reduces pain intensity and spares opioid use after abdominal surgery. Its analgesic effect is 30% lower than NSAIDs, but with less adverse effects. It can be used in combination with NSAIDs and opioids. The main concern is liver toxicity, which is more common in geriatric patients and in those with chronic alcohol consumption.

The NSAIDs such as ibuprofen, ketorolac, naproxen, and COX-2 inhibitors are effective in painful states and possess a broad spectrum of anti-inflammatory and anti-pyretic effects. The NSAIDs increase the risk of gastrointestinal and postoperative bleeding, decrease renal function, and produce an imbalance in wound healing, as well as anastomosis weakening; therefore, their use should be guided by the type of surgery and agreement between surgeon and anesthesiologist.

Ketorolac is widely used during the postoperative period as short-term treatment for acute pain, and is used in combination with opioids for moderate-to-severe postoperative pain; it reduces opioid requirements and, therefore, their adverse effects.

COX-2 inhibitors also reduce postoperative pain, with lower risk of platelet dysfunction and bleeding than NSAIDs, but have been associated with cardiovascular risk in the perioperative period. The risk for renal adverse effects of NSAIDs and COX-2 inhibitors is increasing in patients with previous renal failure, hypovolemia, hypotension, and use of other nephrotoxic agents.

When in postoperative pain there is evidence of neuropathic pain, the indication of antidepressants (amitriptyline, nortriptyline, duloxetine) and antiepileptic drugs (gabapentin, pregabalin) can relieve pain secondary to nervous lesion and different types of neuropathy. Antiepileptic drugs such as gabapentin have been used to suppress both neuropathic and postoperative pain in breast surgery and hysterectomy.

Corticosteroids have been used as adjuvants to decrease opioid consumption and help to reduce postoperative pain. The most widely used and preferred is dexamethasone because it also has shown beneficial effect in the decrease of postoperative nausea and vomiting.

Perioperative management with ketamine at sub-anesthetic doses has been shown to decrease opioid requirements and pain intensity. At these low doses (0.2 mg/kg) in the postoperative period, it has not shown hallucinations or cognitive imbalance.

### Special considerations

The number of patients undergoing ambulatory surgery has considerably grown in the past few years, owing to the advance in surgical and anesthetic techniques. However, procedure complexity has also been increasingly growing, and inadequate pain control has been demonstrated in these procedures, which causes hospital stays and readmissions to
increase. The incidence of moderate-to-severe pain remains at 25-35%, owing to the fact that postoperative analgesia is based exclusively on medications such as paracetamol and NSAIDs, with their previously mentioned limitations.

Exacerbation in chronic pain

Patients with chronic pain conditions require a specific plan for postoperative pain management, particularly those taking large doses of analgesics. Postoperative pain management can be difficult in opioid-tolerant patients, since initial assessment and therapeutic approaches are usually inadequate. These patients will usually require higher doses, and contacting the pain-specialist physician is therefore suggested for adequate management. Patients taking analgesics should continue doing so as usual until before the surgery, except for NSAIDs or COX-2 inhibitors, which must be preoperatively withdrawn. If patches are used, they should be removed during surgery and in the postoperative period. Transition of all chronically taken medications should be made to be intravenously administered.

CONCLUSIONS

Perioperative pain control is one of the main challenges, not only for the anesthesiologist, but for all the healthcare personnel involved in the care of the patient undergoing any type of surgical intervention.

Women’s oncologic conditions are alarmingly on the rise; however, implementation of opportune detection programs has offered the possibility to establish an early diagnosis in many cases. This implies the performance of surgical procedures that, in spite of allowing for the survival and disease-free period to be significantly increased in this group of patients, entail a larger challenge since improving the quality of life becomes necessary, including, of course, the management of both acute and chronic pain as a priority. Avoidance of the painful stimulus appearance is well known to have short, medium, and long-term implications, and knowing the mechanisms participating in the generation of pain is therefore necessary in order to adopt the required strategies that allow for adequate control to be achieved, and in this way have an impact on patient prognosis and quality of life. Thus, modifying our approach from a mere anesthetic act into a series of perioperative systematized pain-control strategies becomes essential.

DECLARATION OF INTEREST

The authors declare not having any conflicts of interests relevant to this manuscript.

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