Chapter

# Chronic Postoperative Pain

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## Abstract

Understanding the definition of pain has imposed numerous challenges toward pain practitioners. The pain experience phenomena are complicated to understand, and this construct goes beyond biomedical approaches. Persistent pain as a disease implicates changes that include modified sensory feedback within the somatosensory system. It has been documented that different anatomical restructuring in nociceptive integration and adaptations in nociceptive primary afferents and perception conduits are present in persistent pain situations. Chronic postoperative pain (CPOP) is known as a particular disorder, not only associated with a specific nerve damage or manifestation of a unique inflammatory response but also with a mixture of both. The occurrence of CPOP varies substantially among the literature and depends on the kind of procedure. There are reports informing that 10 to 50% of the patients undergoing common procedures had CPOP, and 2 to 10% of patients complained of severe pain. Systematic review has been performed trying to identify the Holy Grail, none showed sufficient evidence to guide CPOP treatment, and multimodal approaches must be tried in large randomized controlled trials (RCTs) to provide robust evidence as evidence-based management for CPOP still lacking.

**Keywords:** chronic, pain, postsurgical, persistent, postoperative

## 1. Introduction

It is necessary to fully understand the latest definition of pain, and it is well implied that this subject has imposed several challenges toward pain practitioners, requiring some adjustments over the years. The revised International Association for the Study of Pain recommended that the concept of pain should be revised to "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage." It is well known that this definition has suffered changes over the years because of the complexity of this experience where it can differ broadly in intensity, quality, and duration and has varied pathophysiology mechanisms and implications [1–4].

Pain as an aporia. The approach toward the treatment of pain needs to be multidisciplinary, that is why all the patients with persistent pain invite a clinical judgment of psychosocial susceptibility. The pain experience phenomena are very complex to

understand; in these recent years, we still practice a linear (biomedical) approach where we do not find success in terms of treatment; this construct goes beyond biomedical approaches. We as doctors need to accept that there are various cases where the solution is beyond our expertise and very difficult to comprehend. That is why currently the concept of pain constitutes an aporia (paradox), but as pain physicians we have the ethical obligation to engage this disease to benefit the patient that is experiencing pain [3–5].

Persistent pain as a disease implicates changes that include modified sensory feedback within the somatosensory system. It has been documented that different anatomical restructuring in nociceptive integration and adaptations in nociceptive primary afferents and perception conduits are present in persistent pain situations. This pain state involves a biopsychosocial model where the biological aspect is not always the answer; it is well described that pain states defined as "functional" are expressed, and there is no evidence that justifies this pathology, only psychological and environmental causes. There are other complex cases known as nociplastic pain; in this situation, there is no clear evidence of tissue harm causing the triggering of peripheral nociceptors or sign for disease or alteration of the somatosensory system responsible of the pain state [3, 4].

The proposition made by these authors regarding this construct brings up to mind the concept of biopsychosocial framework, where we can talk about the body-mind dualism proposed by Rene Descartes. It is very difficult to define pain, we as doctors try always to rule out potential biological causes that provoke pain, forgetting that sometimes there is a biopsychosocial framework responsible of this incident [2, 3].

Anesthesiologists play an important role in preventing this pathology, and they have all the tools and knowledge necessary to avoid this type of pain. Chronic postoperative pain (CPOP) is known as a particular disorder that not only associated with a specific nerve damage or manifestation of a unique inflammatory response but also associated with a mixture of both [3].

## 2. Incidence

The occurrence of CPOP varies substantially among the literature and depends on the kind of procedure. It has been documented 20–50% for mastectomy, around 50–80% for amputation, and 5–65% for thoracotomy. There are reports informing that 10 to 50% of the patients undergoing common procedures had CPOP, and 2 to 10% of patients complained of severe pain [3].

In 2015, there was a study implemented in 21 European hospitals, and the significant outcomes were a 6-month postsurgical extension. There were reports of modest severe CPOP in 24% of patients and exceedingly severe CPOP in 16% of patients. At the end of a 12-month follow-up, the incidence of CPOP was reduced 12 to 24% depending on the duration and the intensity of pain in the first 24 hours. With this information they concluded that the pain duration in the first 24 hours is considered as a risk factor for the progress of CPOP [3].

CPOP is a well-defined pathology that affects patients who were exposed to a certain type of surgery (affection of 5 to 75% of surgical patients). This type of pain is very important to consider because it affects importantly the quality of life and results in patient disability and mandate additional health and social expenses. When the evidence points out that the cause of the pain is neuropathic the condition

exacerbates, with an occurrence of CPOP fluctuating from 6 to 68% of the cases, differing on distinct surgery scenarios. The first publication that identified prior surgery as a cause of chronic pain came from a pain clinic in Northern England in 1998 where Chrombie et al. found that almost one in four patients attributed their pain to an operation. Since that time, it has been shown that depending on the type of surgery, the incidence of CPOP is anywhere between 5 and 85%. The frequency over the last years has not changed over time, the exact mechanisms of CPOP remain uncertain, and the treatment continues to be a challenge [3, 6, 7].

## 3. Criteria for diagnosis

The criteria for CPOP suggested by Macrae and Davies in 1999 are as follows:

1. The pain must have established following surgery.

2. The pain is of at least 2 months in length.

3. Other sources of pain have been eliminated.

4. The likelihood that the pain in continuing from a preexisting problem must be investigated and exclusion attempted.

The recently suggested criteria are as follows:

1. The pain progresses after a surgical event or rises in intensity after the surgical process.

2. The pain is of at least 3–6 months duration and significantly affects quality of life.

3. The pain is a perpetuation of acute postsurgery pain or progresses after an asymptomatic stage.

4. The pain is contained to the surgical field, projected to the innervation zone of a nerve located in the surgical field, or referred to a dermatome.

5. Other causes of the pain should be eliminated [3, 6, 8].

## 4. Risk factors

Some circumstances allow the establishment of CPOP, an important risk factor in the type of surgery, although there are some other factors to be included in these perpetuation of conditions such as acute severe postsurgical pain, biopsychosocial affection, demographics, and lack of control on the intensity of pain in the near postoperative stage. Actual data informs us about the gross number of surgeries made annually throughout the world. This gives us an idea of the estimate for the general frequency of 10% for CPOP, meaning that around 23 million patients per year are suffering with this painful situation [3].

### 4.1 Abdominal surgery

In 2014, a report integrated liver donation patients that had a frequency of CPOP of 31% in 6th month and 27% in 12th month and concluded that several risk factors were involved, detecting female gender, young patients, and psychological distress associated with pain states as potential elements for the development of CPOP. In 2015, a retrospective study documented a CPOP frequency of 17% following colorectal surgery and concluded that potential risk for CPOP were redo surgery for anastomotic leakage, inflammatory bowel disease, and acute severe pain. Similarly, in 2016, an analysis found that women who encountered an abdominally based autologous breast reconstruction surgery found a frequency of CPOP of 23–24% in a 6–12 month follow-up; they concluded that the leading cause for the development of CPOP at 6 months is poor control of severe acute pain in the first 24-0 hour post-surgery [3].

### 4.2 Breast surgery

Modern analysis has determined a frequency of CPOP of 30–60% with an existence of moderate to severe pain of 14%. It is well documented that preoperative distress may be considered as a key element for CPOP progression, and another nonsignificant risk factors are <65 years of age, breast reconstructive intervention, axillary lymphadenectomy, bad control of acute severe pain in the postsurgical period, inferior presurgical diastolic blood pressure, and signs of somatosensorial damage associated with pain at 1 week [3].

### 4.3 Cardiac surgery

Actual reports in patients after sternotomy document a frequency of CPOP at 3 months to be 43%, diminishing substantially over time reporting 11% at 12 months and 3.8% at 5 years. In 2016, several authors concluded that a positive neuropathic sign like hyperalgesia around the sternotomy wound on day 4 of surgery was not linked with CPOP at month 4th and 6th. However, they concluded that the biopsychosocial sphere, age, gender, obesity, complex surgeries, history of previous procedures, osteoarthritis, and poor management of acute severe pain in the postsurgical period may be linked with and increased risk for development of CPOP [3].

### 4.4 Hysterectomy

A couple of studies discovered a global frequency of CPOP of 26% at 6 months after laparoscopic or vaginal hysterectomy and a rate of moderate-to-severe CPOP of 10.2 and 9.0%, correspondingly, at 3 and 12 months after these surgical approaches. In a report developed in 2015, they found that procedures performed with this methodology had a strong relationship with CPOP if they had a story of tobacco usage, acute severe pain in the first hours of the postsurgical period, history of infection related to the procedure, and anxiety associated with the surgery [3].

### 4.5 Inguinal hernia surgery

A study conducted in 2015 associated with inguinal hernia surgery after 1 year of the surgical procedure reported a frequency of CPOP of 43% in patients aged

18–40 years old, 29% in the 40–60 age interval, and barely 19% for patients with 60 years and above. In patients where the inguinal repair was made with mesh, there is a strong link with CPOP development with a frequency of 9.3% at 3 months and intensity of CPOP was related with robust hemodynamic preoperative changes [3].

### 4.6 Total knee arthroplasty

The latest data on osteoarthritis patients document a CPOP frequency of 58%. At 2014, an analysis discovered a strong relationship with severe pain intensity throughout a knee active flexion an extension exercise preceding a total knee arthroplasty (TKA) with moderate to severe pain at 6 months. A meta-analysis conducted by Lewis et al. followed patients during 3 months to 7 years undergoing TKA; they discovered that there was a strong linkage with CPOP and alterations in the biopsychosocial sphere, presurgical knee pain, other chronic pain states associated with current pathology, and catastrophizing [3].

### 4.7 Thoracic surgery

Actual reports related to this type of approaches document a frequency of 57% for CPOP at 3 months, 39–56% at 6 months, and 50% at 1 year. Regarding other thoracic approaches that are minimally invasive like the ones that are video-assisted have a lower frequency of CPOP that extend 11–30% [3].

### 4.8 Thyroidectomy

Evidence on a report of 2016 sustains a frequency of 37% for CPOP at 3 months preceding minimally invasive video-assisted thyroidectomy. Different studies document a frequency of neuropathic pain preceding thyroidectomy of 12–9% at 3rd and 6th month, respectively. There is a strong linkage with presurgical anxiety and doubt respecting the procedure with the development of CPOP [3].

## 5. Key definitions

Acute pain is considered as a particular state where the patient experiences a biopsychosocial reaction to tissue lesion related to inflammatory states, and it can experience discomfort and the management can be very complex. Generally acute pain is limited to a time interval but, in some cases, it may perpetuate and transform in chronic pain. One of the purposes of acute pain is human preservation, and it limits conducts that place the patient in danger and promotes tissue healing [5].

Chronic pain is characterized as pain that endures beyond tissue healing and the related metabolic and inflammatory disruption in the body. This kind of pain affects completely the biopsychosocial sphere and promotes patient disability and hospital costs in an important manner [6].

Persistent postsurgical pain is documented in 10–50% of patients that undergo surgery; depending on the magnitude of the surgery some of these patients will experience acute severe pain, if this initial situation perpetuates patients can develop chronic pain. It is well documented that one of the main factors for persistent postsurgical pain is poor control of acute pain in the first hours of the postsurgical event. The IASP's classification system for chronic pain syndromes makes a particular

description as "a persistent pain state that endures two or more months of the surgical event that cannot be explained by other causes." This is accompanied by different changes that affect the somatosensorial system that lead to central and peripheral sensibilization that finally will manifest as chronic pain and worsen the patient's quality of life [6].

## 6. Factors related to the development of CPOP

There are different causes that perpetuate CPOP, and there is an argument that places an important relationship of acute severe pain associated with nerve injury as a crucial element of this continuum and subsequently the presence of neuropathic pain. The surgeries that are related with CPOP in this circumstance (nerve injury) are breast reconstruction, thoracotomy, and amputation. It is important to mention that there is not always evidence of nerve damage in patients with CPOP, and those who have nerve damage will not develop CPOP constantly. There is evidence that one of the principal elements of CPOP progression is repeated and intense triggering of primary afferents which encourages peripheral and central sensitization [3, 6, 7].

If the outcome of the surgery is nerve injury the patient will experience inflammatory changes that will encourage electrical discharges and early ectopic events in the nociceptive pathways. There may be observed adjacent propagation of intact nociceptive afferents nearby areas innervated by injured afferents, and this added to changes induced by damage progression in the somatosensorial system developed by this continuum of events posterior to perioperative pain incitement [2, 5]. CPOP progression is defined by neuroplastic changes resulting from neurotrophic factors and the interface neuron-microglia, and in association with the outcomes of inhibitory modulation. If this particular situation is not managed, CPOP can progress and manifest different alterations that can develop a complex pain syndrome that perpetuates over time and the treatment may impose an important challenge [3, 6, 7].

### 6.1 Chronicity of acute pain

This event leads to variations in the peripheral and central somatosensory system associated with inflammatory and biochemical modifications that in combination aggravate this pain syndrome. It has been described several changes in distinct receptors where we can punctuate the erratic activation of N-methyl-D-aspartate (NMDA) receptors that leads to liberation of glutamate in the spinal cord at the dorsal horn originated by peripheral afferents, and additionally ectopic and erratic triggering of nerves injured during the surgical event. These neuroplastic changes lead to peripheral and central sensitization resulting in an exaggerated response to pain [3, 6, 9].

Positive symptoms of neuropathic pain include allodynia and hyperalgesia that strongly suggest signs of central sensitization, and these states frequently express incongruence concerning the intensity and perception of the painful stimulus. Hyperalgesia is usually seen throughout the tissue recovery course; if this event persists and it is allowed to progress, it may be related to CPOP progression. Without a doubt, the degree and length of central and peripheral sensitization and the mechanisms causing disparity among the descendent and ascending pain nociceptive

pathways; these circumstances fluctuate enormously during the progress of acute severe pain and CPOP [3, 6, 9].

### 6.2 Animal experiment basic research

In the 90s of the last century, a specific animal model was designed to recognize mechanisms that are essential for lesion-induced postsurgical pain. A plantar lesion model was described to study particular evidence of the fundamental neurophysiology of lesion-induced pain. Somehow this model describes that many of the mechanisms responsible of pain as inflammation, antigen-induced or neuropathic pain are not responsible for incisional pain and vice versa. A couple of concepts are revealed during an induced lesion, primary hyperalgesia that develops at the side of the incision and subsequently in an area adjacent to the injury when it comes to secondary hyperalgesia after various days once the lesion has established [3, 6, 9].

### 6.3 Spinal sensitization after surgical incision

It has been documented that several elements that are used to avert central sensitization and CPOP progression in other pain models were unsuccessfully after surgical incision. The initial reports regarding this model identified that NMDA receptor antagonists were futile in the context of CPOP prevention. Somehow this information guided to the hypothesis that the surgical lesion originates another type of spinal sensitization compared to other pain entities. This type of sensitization is perpetuated after this model (plantar incision) is sustained by the afferent limit of sensitized nociceptors on the non-NMDA/AMPA receptor group, which in conjunction are accountable for no evoked pain and hyperalgesia after surgical lesion. There are several substances responsible of mechanical/heat hyperalgesia that act on the ascending and descending nociceptive pathways, and the stimulation of GABAA and GABAB receptors somehow diminish this response, but there is no evidence on attenuation of no evoked pain by this specific reaction [3, 6, 9].

### 6.4 Peripheral sensitization after incision

In the initial stages of surgical lesion, the reports on plantar incision provide substantial evidence of peripheral C and A delta fiber sensitization in the acute phase. There is analysis in behavior and neurophysiological experiments where muscle nociceptors play a crucial function in the cause of no evoked protecting conduct after surgical lesion. Although a skin surgical lesion without involvement of muscle tissue lesion seems to be accountable for promoting mechanical hyperalgesia posterior to surgical lesion. This confirms that a muscle injury is not required for the appearance of positive signs of neuropathic pain on the patient [3, 6, 9].

### 6.5 Neuroplastic changes in the brain after incision

Actual evidence confirms that presurgical or postsurgical exposure to distressing elements like immobilization and force swimming test does not make difference on pain awareness to incitements, such as mechanical, hot, and cold, and it somehow delays the period of lesion provoked hyperalgesia after surgical incision. There are reports linked to abolishing stress-induced hyperalgesia by the withdrawal of adrenal gland and impeding the activation of glucocorticoid receptors [3, 6, 9].

## 7. Prevention of chronic postoperative pain

As already mentioned, CPOP has a deleterious effect on the quality of life of the person who suffers from it, causing important economic, social and family repercussions. The risk factors that predispose to the presentation of this entity have already been enumerated, and how it can be added to each other for its presentation. That is why efforts should focus on correcting modifiable causes, such as the characteristics of the surgery, anesthesia techniques, and the use of pharmacological prophylaxis [10].

Although it is not a certainty that CPOP can be avoided, diverse reports have determined that the frequency is lower when risk factors are identified [2]. Preoperative factors, such as localized pain far from the surgical site, chronic use of opioids, and mood disorders such as anxiety and depression, will alert about the patients who need multimodal strategies such as regional anesthesia, hyperalgesic drugs, etc. [11]. The objective will then be to reduce the mechanisms of central and peripheral sensitization [12]. Regional anesthesia, peripheral nerve blocks, and intravenous infusions of various anesthetic adjuvants have been shown to be beneficial in the prevention and reduction of chronic postoperative pain [12].

Among the most accepted and recommended drugs are NSAIDs, as long as there is not contraindication, and in conjunction with a protective medication for the gastric mucosa, or a selective COX2 (cyclooxygenase-2) inhibitor (maximum 7 days, and do not use in cases with increased risk of a thrombotic event) [11].

Intravenous infusions of local anesthetics such as lidocaine have recently shown good results in the prevention and control of immediate postoperative pain, which it means into a lower prevalence of persistent pain after recovery. Some study protocols talk about loading doses followed by infusions of around 1–2 mg/kg/h with encouraging results [11]. There is no evidence indicating that gabapentinoids reduce or prevent CPOP, so they are not recommended [11, 13, 14]. Although no prophylactic role has been found in the use of gabapentinoids, they have been used successfully in the long-term treatment of persistent postoperative neuropathic chronic pain [15, 16].

The use of ketamine has been justified by its properties at the NMDA receptor level and its antagonism in the dorsal horn of the spinal cord. In combination with other agents, it has been shown to be effective and safe [16].

The mechanism of local anesthetics in chronic postoperative pain perhaps due to the decrease of neuronal inflammation and glial activation, avoiding chemical, structural, and functional changes [15].

The use of opioids alone for the postoperative period has not been associated with reductions in the incidence of postoperative pain; to the contrary it produces opioid-induced hyperalgesia and prolonged use after surgery. The use of opioids in multimodal therapy with NSAIDs is recommended to reduce the effects of acute inflammation induced by cyclooxygenases and the sensitization of peripheral nerve fibers [17].

Regional anesthesia and nerve blocks are perhaps one of the most useful measures for the prevention and management of CPOP. It is recommended that, when it is identified a patient with risk factors for developing CPOP, regional anesthesia can be prioritized whenever possible or, otherwise, general anesthesia using local anesthetics such as lidocaine, alpha agonists (dexmedetomidine), inhibitors of NMDA receptors (ketamine), and plexus or peripheral nerve block techniques, to maximize the analgesic effect during the intraoperative period and during the acute phase of post-surgical recovery.

In abdominal surgeries, for example, improvement in acute postoperative pain and a lower incidence of CPOP have been found with the use of a transverse abdominal plane block plus placement of a continuous perfusion catheter [8]. Neck procedures under general anesthesia and a bilateral superficial cervical plexus block have been described with good results and lower levels of acute postoperative pain. This strengthens the idea that maintaining pain control during the first 24 hours after surgery reduces the risk of pain chronicity. In spinal surgery, erector spinae blockade techniques have been described for postoperative pain control with good long-term results [5].

Prevention strategies must be applied in those patients considered to be at high risk, perform a complete preoperative evaluation before and after the procedure, and develop preventive strategies establishing an appropriate therapeutic plan for each particular patient.

## 8. Diagnosis of chronic postsurgical pain

It has currently been considered that it is mandatory to identify the risk factors and the possibilities to prevent CPOP, because it has been studied by different authors as a preventable sequel and some others classify it as iatrogenic, since the triggering mechanisms are already known. The diagnosis of this syndrome is already described in the International Statistical Classification of Diseases (ICD-11) of 2019 [18]. One of the most common and devastating forms of presentation is postsurgical chronic neuropathic pain, both for intensity levels as well as functional alterations for the patient.

The medical history is an essential part of the patient evaluation. The characteristics of the pain, intensity, triggering and mitigating agents, as well as the history of pain prior and after the surgical procedure, in addition to the functionality report, will be important indicators that will guide us in the diagnosis. The use of scales to assess the pain, visual analog scale, or numerical analog scale can be a useful guide in the follow-up of the cases. Patients with limited pain communication, such as patients with cognitive impairment or who have a condition that makes it impossible for them to speak, should not be overlooked. For this, behavioral tools such as Pain in Advanced Dementia (PAINAD), Behavioral Pain Scale, have been created for evaluation of these type of patients [18]. Another aspect that should not be forgotten is obtaining a description of persistent postoperative pain with the degree of functional impairment and the extent of disability in the patient [19]. In the study of Stamer in 2019, the associated variables with persistent postoperative pain 6 months after surgery were found: young patients, with intense pain before the surgical procedure or severe pain in the 24 hours following postoperative recovery. In the gender relationship, men showed a risk 3.6 times greater than women; the most commonly associated surgeries were orthopedic, abdominal, and thoracic related to breast cancer [16, 18, 19].

Diagnostic criteria for this entity have not yet been described; however, the recent definition of the IASP can guide evaluation and timely treatment [10]. The type of surgery also helps to establish diagnostic suspicion, for example, in breast cancer CPOP presents 65% of the time as neuropathic pain, mainly as intercostal neuralgia and post-mastectomy pain syndrome, followed by musculoskeletal pain. Another aspect that should not be forgotten when obtaining a description of persistent postoperative pain is the degree of functional impairment and the extent of disability in the patient [19].

## 9. Chronic postoperative pain management

As we mentioned in previous lines, CPOP may be ominous as patient experience more emotional distress and tends to have higher pain intensity compared to those with an insidious onset, making it even more difficult to manage; biopsychosocial approach is recommended to understand and treat the source properly; rehabilitation programs must be included [10].

Exhaustive clinical examination focusing on identifying sensory dysfunction areas due to nerve damage, previous medical history detailing prior pain medications, impact on quality of life and limitation for daily-basis activity should be considered as first step to chronic pain treatment to identify the mechanisms by which chronic pain is being produced or was produced in the first place; during assessment before any intervention, possible postsurgical complication must be ruled out, complications due to surgical technic or preoperative patient's conditions such as malignancy recurrence or intestinal anastomosis leak are extremely frequent [20]. Once knowing the mechanisms and its etiology, a treatment line can be established based on its causes. Prevention is the cornerstone to avoid the perpetuation of pain; however, in case of CPOP, multimodal treatment would be the ideal choice [21].

One of the main techniques in the management is regional anesthesia, whether applied neuraxially or as peripheral nerve blocks. It has an effect through the modulation of pain to avoid central and peripheral sensitization; this technique has the ability to transform moderate or severe pain to mild, and the purpose is to avoid central sensitization or reduce the probability of it on the long run. Regional anesthesia techniques vary according to each surgical procedure, or the site of pain that the patients specify [22, 23].

Other pharmacological alternatives are gabapentinoids, through the inhibition of the alpha(2) delta unit regulate neuronal excitation, preventing the over excitation and sensitization. However, the adverse effects are significant (dizziness, nausea, vision changes), and relatively high doses are usually required for control or therapeutic efficacy [24]. Alpha2 agonists belong to another group of drugs used to relieve, reduce, and prevent pain, and these effects are produced through an agonist effect on alpha receptors in the spinal cord, causing analgesia and an opioid-sparing consumption produced by synergistic effect, the representative drugs are dexmedetomidine and clonidine, but both have important adverse effects such as sedation. Thus, there are no presentations for alpha2 agonists in the outpatient setup, and they can only be used in the hospital environment under strict surveillance. More scientific evidence is required to investigate the efficacy/safety of this therapy, since there are few important clinical studies that support these effects [25]. COX 2 inhibitors and paracetamol are adjuvants that could be used to reduce and control pain, both are involved in the regulation of the inflammatory response mediated by pro-inflammatory cytokines, by inhibiting the synthesis of prostaglandins, acute-phase reactants whose inhibition could prevent or avoid the risk of perpetuating central and peripheral pain sensitization. Currently, there are no randomized clinical studies which use COX 2 inhibitors and acetaminophen for the treatment of CPOP, though both drugs belong to treatment strategies in a multimodal analgesia scheme [26].

## 10. Conclusions

Above all, opioids and the use of regional anesthesia are probably the first-line treatment strategies for CPOP as they can provide an almost immediate and significant

benefit in the setting of acute severe pain. Within opioids, mild-acting ones such as tramadol as well powerful opioids (oxycodone, buprenorphine, fentanyl) which have numerous presentations and routes of administration for pain control are part of the tool setting of the anesthesiologist in the acute pain scenario. However adverse effects such as sedation, nausea, constipation, and opiophobia limit its uses; it is indispensable for the anesthesiologists in the acute pain scenario to have a robust knowledge of the opioid pharmacokinetics and pharmacodynamics for adequate outcomes, as well a proper training in regional anesthesia and ultrasound management to provide an effective execution of this techniques [27].

Systematic review has been performed trying to identify the Holy Grail, all the interventions included were unimodal, none showed sufficient evidence to guide CPOP treatment, multimodal approaches must be tried in large randomized controlled trials (RCTs) to provide robust evidence as evidence-based management for CPOP still lacking.

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