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NARRATIVE REVIEW

Chronic postoperative pain: ubiquitous and scarcely appraised: narrative review

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Abstract The International Association for the Study of Pain chose pain prevention as the theme for the 2020 Global Year. Chronic postoperative pain is one the many types of pain that can be potentially prevented. It develops or increases in severity after a surgery, persists for at least three months, even after ruling out all other possible causes of pain. To perform the present narrative review, the authors searched the PubMed database using the following keywords ''postoperative pain'' OR ''postsurgical pain'' AND ''chronic'' OR ''persistent''. The present review focused on the incidence, pain development and chronification, and predisposing factors. It also discusses prevention, diagnosis, and treatment of chronic postoperative pain. Awareness of occurrence of chronic postoperative pain and recognizing risk factors is crucial for the day-to-day practice of the anesthesiologist. Hence, numerous surgical patients can have their outcome improved by preventing chronic postoperative pain, a condition scarcely identified and without a well-established treatment.

Introduction: chronic postoperative pain (CPOP)

The International Association for the Study of Pain (IASP) chose 2020 as the Global Year for prevention of pain. We are aware that many cases of pain could be prevented with proper assessment and diagnosis prior to the establishment of central mechanisms that render pain chronic. Hence,

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IASP planned to disseminate strategies for pain prevention to clinicians, researchers, and patients.[1] Indeed, currently, CPOP is the condition that has been drawing most of the attention and is the type of pain in which anesthesiologists play a central role.[2]

CPOP is a pain that results or increases in severity after surgery and persists for at least 3 months, after ruling out any other possible causes, such as infection, tumor recurrence or pain arising from pre-existing conditions. Therefore, CPOP is not part of the natural progress of the disease that prompted the surgery.[3,4] CPOP identification dates back more than 20 years as it was first reported in 1999.[5] Several reviews on CPOP followed this first report, but not much knowledge has been added to pathophysiology, epidemiology, risk factors, and management of CPOP.[6–8]

The most recent publications have focused on determining CPOP risk factors and possible measures to prevent CPOP, as well as pointing out the types of surgery that are more likely to be related to CPOP, but not much success has been achieved.[9]

Recently, IASP and the World Health Organization have launched a joint effort to include CPOP in the new International Code of Diseases (ICD-11), and the condition has now been described as a new disease in the ICD-11. Thus, CPOP is listed as one of the seven categories that subdivides chronic pain.[10]

We believe all anesthesiologists hold critical knowledge and skills that can influence the best postoperative outcome. Thus, this narrative review aims to highlight the latest studies on CPOP and certain strategies that may be relevant for its prevention.

Search strategy

To perform the narrative review, the authors executed a PubMed database search using the following keywords in English: ''postoperative pain'' OR ''postsurgical pain'' AND ''chronic'' OR ''persistent''. The search did not limit the type of study or intervention. All titles and abstracts were analyzed, and we included only the most relevant studies published in Portuguese, English, or Spanish, and the most recently published articles were prioritized.

Incidence

The incidence of CPOP reported in the literature varies substantially. One reason is the presence of several factors affecting CPOP incidence, making it hard to obtain dependable data, even from studies that have more elaborate designs. An additional relevant aspect to be considered is the wide range of incidence reported per type of surgery, for example, 20% to 50% for mastectomy, 50% to 85% for amputation, and 5% to 65% for thoracotomy.[11]

In 2006, an article revealed that 10% to 50% of patients undergoing common procedures had CPOP, and 2% to 10% of patients complained of severe pain. For the authors of that article, the problem was already critical and not fully recognized.[12] A 2015 study performed in 21 European hospitals identified, at the end of a 6-month postsurgical follow-up, the incidence of mildly severe CPOP in 24% of patients, and highly severe CPOP in 16% of patients. At the end of a 12-month follow-up, incidence of mildly severe CPOP decreased to 23%, while highly severe CPOP decreased to 12%. The authors observed that pain duration in the initial 24 hours, more than pain intensity, was a relevant factor for the development of CPOP.[13]

Depending on the surgery, CPOP is estimated to affect 5% to 75% of surgical patients, result in patient disability and anguish, reduce quality of life, and demand health care and high social and therapy costs.[3,9,12] When the pain source is neuropathic the situation aggravates, with an incidence of CPOP ranging from 6% to 68% of cases, depending on the surgery.[14]

Table 1 shows the average incidence of subacute and chronic pain in different surgeries.

Table 1 Frequency of subacute and chronic postoperative pain according to surgical procedures.

Procedure	Subacute pain, up to 3 months (%)	Chronic pain, up to 12 months (%)
Inguinal hernia repair	21–0	29.7
Thoracotomy	70.6	41.2
Sternotomy	40	27
Knee arthroplasty	22.6	18.4
Hip arthroplasty	20	28
Lower limb amputation	67	75
Mastectomy	45	43–56
Gynecological surgery	17	15–40

Modified from de Steyaert A, Lavand'homme P, 2018.[3]

Factors related to the development of CPOP

The mechanism of CPOP has been subject of much investigation. Great emphasis was placed, initially, on nerve injury as a determinant cause of CPOP and, consequently, the presence of neuropathic pain. This is especially true for some types of surgeries, such as mastectomy, thoracotomy, and amputation.[9,12,15] However, not all patients with nerve injury develop CPOP and, in many who do, there is no evidence of nerve injury.[10,16] Currently, CPOP is recognized as a specific condition, not only related to isolated nerve injury or occurrence of isolated inflammatory response, but to a combination of both.[14,17]

It is believed that the primary afferents are largely responsible for the maintenance of CPOP and that their repeated and intense activation induces the occurrence of peripheral sensitization and results in central sensitization. In addition to this, during the intraoperative period nerve injury does occur.

In the aftermath of nerve injury, the occurrence of electrical discharges and early ectopic activities can be observed. The abnormal electrical activity occurs in injured primary afferents and in damaged nerve fiber of cell bodies of the dorsal ganglion but can even be registered in cell bodies of undamaged neurons lying adjacent to the injured nerves. Collateral sprouting of intact nociceptive afferents can be observed, contiguous to zones innervated by damaged afferents, in addition to structural changes in

the central nervous system arising from the continuous perioperative pain stimulus.[16,18,19]

The occurrence of CPOP may be explained by the continuing neuroplastic changes secondary to the neurotrophic factors and the interaction between neurons and microglia, in addition to the effects on inhibitory modulation. Microglia intracellular signaling undergoes continuous upregulation and activation, promoting permanent stimulation of neurons and, consequently, pain perception.[20]

CPOP is clinically characterized by changes in pain sensitivity, initially related to the surgical wound and, later, transformed into a complex pain syndrome that increases in intensity in days, weeks, or months after the procedure.[21]

Chronicity of acute pain

Tissue injury caused by surgery plays a fundamental role in the development of CPOP, leading to major changes in the peripheral and central somatosensory circuitry, as previously described. The underlying biochemical changes and the subsequent events will be briefly described below.

N-Methyl-D-Aspartate (NMDA) receptors are activated after sustained and intense release of glutamate in the spinal cord dorsal horn caused by peripheral afferent inputs, but also after fast firing from nerves injured during surgery. The high permeability to calcium of the NMDA receptors activates several metabolic cascades that can lead to synaptic plasticity and, in more severe cases, cytotoxicity and neuronal apoptosis. Glutamate, NMDA receptors, and calcium influx play an important role in the chronicity of pain.[22]

Neuroplasticity involves neuronal and synaptic changes resulting from modulation (reversible changes in neuronal excitability) and modification (irreversible changes in neuronal structures, receptors, and ion channels), leading to altered response to pain.[20]

Central sensitization symptoms include allodynia and hyperalgesia. They signal a discrepancy between the intensity and perception of the painful stimulus.[20] Hyperalgesia is normally observed during the tissue healing process, however, if it persists beyond natural recovery time, it can be associated with CPOP development.[23,24] In individuals subjected to similar stimuli, the magnitude and duration of central sensitization and the mechanisms resulting in the imbalance between inhibitory and excitatory processes vary greatly during the development of acute pain and CPOP.[25]

Lately, it has been questioned whether CPOP is a continuation of acute postoperative pain, or whether there is an interval between both. It is acknowledged that there is a period of subacute pain during which its management has been neglected. This pain can last for several weeks, have a negative psychological impact, contribute to the process of central sensitization, and is associated with hospital readmission and delayed postoperative recovery.[3,25–27]

Predictive factors for CPOP development

Risk factors for CPOP development have been extensively investigated and those that can be modified are particularly relevant. They are not independent, but rather, interconnected, enhancing the possibility of CPOP development, as for example, being a woman, presenting preoperative depression and chronic pain, and undergoing radical mastectomy.[3,22]

Some factors have already been extensively reported, such as: female gender, young adult age group; presence of severe preoperative pain; preoperative use of opioids and preoperative psychological symptoms, such as anxiety, catastrophizing, depression, and post-traumatic stress syndrome.[3,28–31] A time-based classification of risk factors is widely used: preoperative (women, young adults, fibromyalgia, preoperative pain for more than 30-days, preoperative opioid use, catastrophizing, anxiety, depression, post-traumatic stress, alexithymia, genetic predisposition, quantitative tests of positive pain); intraoperative (surgical technique, extension of trauma, nerve injury, surgery duration); and postoperative (intensity of postoperative pain, radiotherapy, chemotherapy, psychiatric comorbidities).[3,12,15]

More recently, risk factors have been classified into five main categories, depicted in Table 2.[22,32,33]

CPOP prevention

It is often questioned whether CPOP can be prevented and how can we perform it. To date, there are no drugs or procedures that allow us to say with conviction that this is possible, since there are several factors contributing to CPOP establishment and development. Anesthesiologists are requested to identify risk factors, analyze the already available evidence on use of prophylactic drugs, individualize the therapy, and effectively treat acute and subacute pain. However, we cannot forget the crucial role of the surgeon in the prevention of CPOP.[3,22]

Regional anesthesia techniques can favorably impact the outcome of the surgical patient, particularly concerning pain. Anesthesia blockades can prevent central sensitization by decreasing nociceptive afferent stimuli to the dorsal horn of the spinal cord. Epidural anesthesia and paravertebral block were shown to be valuable in reducing the incidence of CPOP in thoracic and breast surgeries, respectively.[34,35]

Evidence shows that spinal anesthesia plays a preventive role for CPOP in patients submitted to C-section. Also, continuous intravenous infusion of lidocaine was shown to be useful for preventing CPOP after breast cancer surgery.[35]

Drugs and administration routes used for preventing CPOP

Numerous drugs have been used and evaluated for preventing CPOP, but none showed very encouraging results. Amongst all, ketamine was the most studied and, in indeed, has shown the most promising results. As previously mentioned, IV lidocaine can help prevent CPOP in selected procedures, opioid-free anesthesia technique has a potential preventive effect that requires additional investigation; memantine and nefopam need further studies; and epidural analgesia has shown modest preventive effect in some studies. Alternatively, the use of gabapentinoids, glucocorticoids, non-steroidal anti-inflammatory drugs, antidepressants, local anesthetic agents, local infiltration, transversus abdominis plane block, and thoracic paravertebral block, until now, have shown no or inconclusive

Table 2 Postoperative chronic pain risk factors.

A. Demographic and lifestyle factors
Age (young adults).
Gender (female).
Marital status (single).
Educational level (low).
Socioeconomic level (low).
Secondary morbid gain.
Obesity.
Smoking.
B. Genetic factors
Associated with complex genetic trait with heritability ranging from 30% to 70%. Genetic mutations such as sodium and potassium ion channels; purinergic receptors; COMT (Catechol-Ortho-Methyl Transferase, that catabolize catecholamines); OPRM1 (precursor of μ protein receptor) and GCH1 (responsible for producing relevant enzymes).
C. Clinical factors
Surgical factors: technique (laparoscopic vs. open approach); duration of procedure; anesthesia technique (general vs. regional); nerve injury.
Analgesia treatment (systemic vs. spinal or regional, preemptive).
Surgical complications and revisions.
Comorbidities (irritable bowel syndrome, rheumatoid arthritis, Raynaud syndrome, peripheral neuropathy, among others).
Pre-existing disabilities.
D. Pre- and postoperative pain
Chronic pain previous to surgery (pre-existing long-term and high intensity pain) increases CPOP risk.
Severity of acute postoperative pain, particularly during the first 5 postoperative days is a highly predictive factor for CPOP.
E. Psychological factors
Fear or anxiety
Depression
Catastrophizing
Alexithymia
Post-traumatic stress
Vulnerability

Modified from Glare P, Aubrey KR and Myles OS, 2019[22]; and Schug AS and Bruce J, 2017.[32]

evidence of prophylactic effect on CPOP in procedures other than breast and thoracic surgery.[3,34,35]

Treatment tailoring

Managing the treatment of each patient according to their risk factors and type of pain stimulus related to the procedure seems to be the key for CPOP prevention. The analgesic regimen should be tailored, both to prevent and to treat postoperative pain, according to the profile of the anticipated or pre-existing pain, either due to increased excitation or inefficient inhibition.

Patients with psychological risk factors should receive pharmacological or psychotherapeutic interventions prior to the procedure. Patients must be stratified according to the inflammatory state of the procedure to provide analgesia during the required time, which may extend beyond the hospitalization period.

We should be alert to chronic opioid users as they are likely to develop CPOP. In these cases, it is recommended to reduce 50% of the opioid dose preoperatively, and/or that ketamine be used in the perioperative period.[3]

Progression from acute to chronic pain

While it is unknown whether acute pain presents continuous progression to chronic pain, the fact that subacute pain can last for several weeks postoperatively has been well defined; its treatment has been little valued; and that, depending on the time and intensity of the pain, subacute pain becomes a predictive factor for CPOP.[25,27]

Analogous to what occurs in hernia repair, postoperative pain severity and incidence may increase in the subacute period, likely due to neuropathic mechanism.[36] Similarly, neuropathic pain can be observed in 8% of patients undergoing thoracotomy in the immediate postoperative period, and after a few months, the incidence may increase to 22%.[37]

Patients submitted to knee arthroplasty and presenting severe postoperative pain that was not relieved in the first four postoperative weeks were more likely to endure pain at the end of the third month.[38] Another prospective observational study, with a follow-up of 12 months, conducted in orthopedic surgeries, reported a high number of patients with pain complaints after hospital discharge and without effective treatment. The study also emphasized the role of subacute pain after hospital discharge in the occurrence of CPOP at the end of the 12-month follow-up and draws attention to the importance of effective pain treatment and routine patient reassessments after hospital discharge.[39]

To adequately monitor the presence of subacute pain after discharge, innovative transient pain clinics have been proposed (Figure 1). This allows making the connection between treatment of acute postoperative pain and treatment of chronic pain, when the former is identified. At-risk patients should return to the clinic between 6 and 12 weeks after discharge to review treatment and be referred to other services, such as physical therapy, mental health, multidisciplinary chronic pain services, and early intervention procedures, whenever indicated.[22]

The role of the surgeon on CPOP

Of all forms of prevention of CPOP, the only one that is totally effective is avoiding surgery.[3] There is a high incidence of CPOP in some specific types of surgery, as previously mentioned. In cosmetic surgeries, for example, as reported in a research on breast surgeries, CPOP occurred in up to 44% of patients, leading to dissatisfaction and regret for many of them.[40]

The surgeon plays an extremely important role and must provide all information about the occurrence of CPOP to patients at risk; whenever possible, use minimally invasive techniques; prioritize the preservation of nerve integrity; and remember that the surgeon's experience, overwork, surgical complications, and surgery revisions affect CPOP incidence.[41]

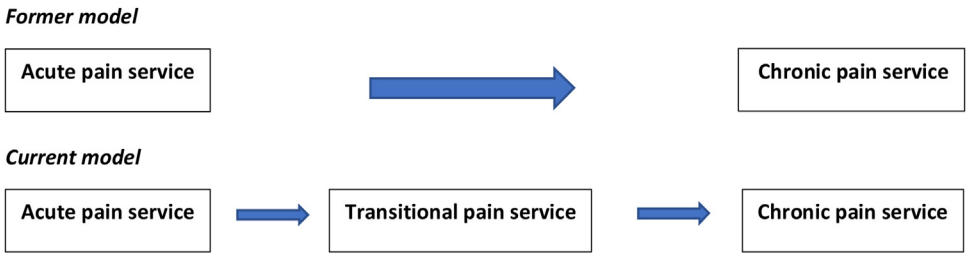

Figure 1 Transitional pain clinic.
Modified from Myles GP, 2019.[21]

Some theories have been proposed to explain failure or inconsistent results associated with preventive measures for CPOP. It is well established that a single intervention does not have a major impact on CPOP prevention since multiple mechanisms and different levels of nociception are involved on CPOP development.

Another important aspect to be considered is that all the processes that generate nociceptive impulses and peripheral sensitization do not cease at the end of the surgery or in the first days of the postoperative period. Finally, in the vast majority of studies, patients have undergone surgery without having their risk factors previously stratified.[40]

Diagnosis

CPOP becomes a complex, multidisciplinary pain syndrome, increasing in intensity in days, weeks, and months after surgery. Neuropathic descriptors such as hyperalgesia, dysesthesia, and allodynia are common, but they may be absent in patients submitted to certain surgeries, such as orthopedic procedures. Changes in mood, sleep, and quality of life, and the presence of anxiety, depression, catastrophizing, and stress are also frequent.[22]

As in any patient with pain, the practitioner should encourage patients to self-report what they understand as their painful experience. Anamnesis should collect data on pain, regarding location, time profile, intensity, alleviating and aggravating factors, and concurrent symptoms. It is also necessary to inquire patients' medical history, identify the presence of past and current diseases, past surgeries, treatments previously used to control pain and the outcome of these interventions. It is interesting to assess patients' functional history, such as how symptoms interfere with mobility, day-to-day activities, interpersonal relationships, sleep, and mood.[42]

Complaint-oriented physical examination provides important data for CPOP diagnosis. Often there is discrepancy between patient complaints and physical examination findings, and occasionally redoing tests already performed is required.[42]

Concerning pain assessment, the painful area must be inspected and palpated. A detailed evaluation of dermatomes, motor function, tendon reflexes, muscle tone and strength, gait and balance are performed in sequence, based on location of the complaint.[42]

Sensory evaluation is an especially important part of physical examination for suspected neuropathic pain, which is often the case in CPOP. As part of the recommended minimum neurological examination, touch sensation should be tested by gently applying a cotton ball to the skin, pain sensation by stimulation with sharps, such as a needle, thermal sensation using hot or cold objects, and vibration sensation with a 128 Hz tuning fork. When the pain is unilateral, the affected area should be compared to the same contralateral area; when the pain is bilateral, the assessment must compare pain in proximal to distal areas.[42]

Treatment of CPOP

As any type of chronic pain, the treatment of CPOP is challenging. Evidence is still lacking and controlled randomized studies are required to establish the benefits of the several currently proposed treatments.[3,16,22] Similarly to non-cancer pain conditions, treatment based on pathophysiology may be useful for CPOP.[43]

Numerous attempts to treat CPOP have been carried out with drugs and procedures, such as anticonvulsants, antidepressants, local anesthetics, opioids, capsaicin, NMDA antagonists, epidural block, neurotoxins, acupuncture, physical exercises, spinal and magnetic neurostimulation, revision surgery, laser, mirror therapy, and interventionist techniques. Thus far, however, the beneficial impact of each technique cannot be safely stated, as previously discussed.[3,20,22]

Final considerations

The treatment of pain today is considered a fundamental human right, and according to the American legal system, inadequate pain management can constitute medical negligence. Although this claim is based on specific American laws, they can, by analogue interpretation or even by analogy in bona partem, be applied to most scenarios. Among the potential factors of negligence, there is failure by the physician to assess the patient's pain, insufficient or inadequate supply of analgesics to the patient, pain treatment failure, and even the failure to refer the patient to a pain management specialist.[44]

There is a close correlation between inadequately treated acute postoperative pain and CPOP[25,27,45] but, likewise, we realize that in this scenario there are barriers hampering adequate postoperative analgesia. Among these we can list those related to the physician and the nurse, those related to the patient, and tolerance to opioids. Apart from anesthesiologists, other health professionals receive insufficient training for prescribing opioids, therefore they

have unsatisfactory understanding of the complex mechanisms of pain, in addition to not being familiar with pain assessment.[45]

Patients, in turn, do not appreciate the importance of multimodal treatment, struggle to accurately describe their pain and fear using opioids. Chronic opioid users are opioid tolerant, which represents a sizable hurdle to adequately provide pain control.[45]

CPOP is a serious biopsychosocial condition deserving urgent care, for once CPOP is installed its management is challenging, significantly affecting patient quality of life. All studies are aimed at prevention, but not much progress has been made in this area. Excellent techniques and agents are available for acute postoperative pain treatment and can be a feasible CPOP prevention tool. More recent recommendations for long-term pain management of surgical patients, particularly those presenting signs of development of CPOP, have shown reassuring results. Ongoing investigations are assessing new treatment regimens for CPOP such as anti-nerve growth factors, Nav1..7 sodium channel antagonists, and epigenetics, which delves into modifying the functioning of genes.[3,11,17]

Acknowledging the existence of CPOP and its well-established risk factors is crucial for the anesthesiologist's daily practice. By using this knowledge, we can impact the outcome of many patients submitted to routine procedures and who, depending on how they are managed, can evolve to CPOP, a disease that is poorly understood now.

Nearly 60 million surgeries are performed annually in North America, Europe, and Brazil. Among these surgical patients, 5% to 75% may develop CPOP. This is a major challenge requiring greater awareness and commitment from everyone, including surgeons and anesthesiologists.

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Conflicts of interest

The authors declare no conflicts of interest.

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