

Chronic postoperative pain: pathophysiology, risk factors and prevention*

Dor crônica pós-operatória: fisiopatologia, fatores de risco e prevenção

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SUMMARY

BACKGROUND AND OBJECTIVES: Chronic postoperative pain (CPOP) prevalence is high, and is manifested both after minor and major surgeries. This subject has been increasingly studied. This study aimed at describing major aspects of this syndrome.

CONTENTS: CPOP mechanisms, risk factors for its development, prevention and pain treatments are described.

CONCLUSION: CPOP impacts patients' quality of life, is difficult to treat and the best approach is to prevent it. With a better understanding of pathophysiological bases for perpetuation of pain after a surgical procedure and of risk factors, new treatment options are appearing. The real benefits of preventive drugs are being increasingly studied. To prevent pain, surgical teams and patients have to be aware of the risks of each procedure, not only in the immediate postoperative period but also in the long run.

Keywords: Chronic pain, Postoperative period, Prevention, Risk factors.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A prevalência da dor crônica pós-operatória (DCPO) é grande, acometendo tanto cirurgias de pequeno porte como as de

grande porte. Esse tema vem sendo estudado cada vez mais. O objetivo deste estudo foi descrever aspectos importantes sobre essa síndrome.

CONTEÚDO: Descrevem-se os mecanismos da DCPO, os fatores de risco para seu desenvolvimento, a prevenção e o tratamento da dor.

CONCLUSÃO: A DCPO afeta a qualidade de vida dos pacientes, é de difícil tratamento sendo a medida mais eficaz a sua prevenção. Com o melhor entendimento das bases fisiopatológicas da perpetuação da dor após um procedimento cirúrgico e dos fatores de risco, novas opções para o seu tratamento estão surgindo. Os reais benefícios da utilização de fármacos usados de forma preventiva estão sendo cada vez mais estudados. Na prevenção da dor as equipes cirúrgicas e os pacientes necessitam estar atentos aos riscos de cada procedimento, não somente no perioperatório imediato, mas também em longo prazo.

Descritores: Dor crônica, Fatores de riscos, Pós-operatório, Prevenção.

INTRODUCTION

Chronic postoperative pain (CPOP) has been neglected for a long time by the medical community. Currently, CPOP is being increasingly studied with important evolution.

Although scarcely documented in the literature, CPOP incidence is highly variable and appears both after highly complex surgeries, such as thoracotomy, and after simplest ones, such as inguinal hernia and vasectomy. After surgery, between 5% and 80% of patients evolve to chronic pain, especially after procedures causing nervous injury¹. The incidence after limb amputation is from 30% to 81%; after thoracotomy and inguinal hernia, from 11.5% to 47%; after cholecystectomy from 3% to 56%²; after breast cancer surgery from 10% to 50%^{2,3}; after vasectomy 15%⁴; after C-section from 6% to 18% and after vaginal delivery from 4% to 10%⁵.

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The broad variation of incidence may be associated to several definitions used for CPOP in different studies^{6,7}. Macrae defines CPOP as pain after surgical procedure lasting for at least two months, unrelated to pre-existing pain and without other defined causes (such as, for example, infection)⁸. Other causes for such variability in the incidence of CPOP are evaluation and interpretation of types of painful syndromes and different study designs⁷. Chart 1 describes some examples of CPOP.

nociceptive stimulation transmission and recruits non-nociceptive stimulations to the pain pathway. Kinase-C protein and nitric oxide (NO) activation contributes to increase the excitability of nociceptive neurons⁹. NO induces sensitization of nociceptors, increasing prostaglandin E2 release, inhibiting the action of endogenous antinociceptive substances on peripheral receptors and directly acting on nociceptors. Central sensitization is partially mediated by NMDA receptor activation with

Chart 1- Examples of surgical procedures and evolution to chronic pain

Limb amputation	Stump pain, phantom limb pain, myofascial pain
Thoracotomy	Intercostal neuritis, myofascial syndrome, costochondritis
Mastectomy	Traumatic neuritis, myofascial syndrome, frozen shoulder, lymphedema
Spine	Arachnoiditis, myofascial syndrome
Myocardial revascularization	Traumatic neuritis, costochondritis, myofascial syndrome
Limbs	Complex regional pain syndrome, myofascial syndrome, frozen shoulder
Hernioplasty	Traumatic neuritis

CHRONIC POSTOPERATIVE PAIN MECHANISMS

Chronic postoperative pain mechanisms are complex and not fully understood. Different mechanisms are responsible for different painful syndromes, even in a single type of surgery⁵.

There is the neuroplasticity process, which is complex and in constant change in membrane excitability, reducing inhibitory mechanisms and increasing the excitatory synaptic efficacy⁹. Surgical stimulation, which starts with the incision, is maintained throughout the postoperative inflammatory process and finishes only with surgical healing, causes the neuroplasticity process⁶. There are two types of neuroplasticity: peripheral and central. Peripheral neuroplasticity is responsible for local hyperexcitability of high threshold peripheral nociceptive terminations and is caused by inflammatory mediators released by injured tissues or inflammatory cells, by the activation of intracellular cascades with lower threshold and there may be pain perception with a weaker stimulation. In central neuroplasticity there is synaptic change of the spinal cord with amplification of pain signal¹⁰. A peripheral nociceptive stimulation activates intracellular kinases pathway at the spinal cord dorsal horn changing ionic channels flow and the density of receptors and neurotransmitters. Central sensitization increases activity and density of AMPA and NMDA receptors, leading to a post-synaptic hyperexcitability. The increase of glutamatergic synapses in the spinal cord dorsal horn reinforces

subsequent production of NO¹¹. After central sensitization induction, responsiveness of neurons is increased and even those which normally have ineffective synapse for stimulations, inoculate and activate neuronal pain transmission¹⁰.

The mechanism of postoperative pain propagation by direct peripheral nervous injury is highly variable. The injury of major nerves located in the surgical field of most procedures is probably a pre-requisite for the development of CPOP¹⁰. In a thoracotomy study with and without intercostal nerve protection, pain evaluation after 2 to 7 days has shown a lower pain score in patients who had their intercostal nerve protected, however this was not observed one month after surgical procedure¹⁵. In a different study, authors carried out an electrophysiological study in patients submitted to thoracotomy before and three months after procedure. They have not observed association between intercostal nerve injury and pain or sensitivity change after three months of follow-up¹³.

Risk factors

Several factors contribute to chronic postoperative pain¹⁴⁻¹⁷.

- Preoperative factors: pain lasting more than one month, psychological, genetic and diabetes mellitus;
- Intraoperative factors: nervous injury, incision site and type, duration, repeated surgery and complications;
- Postoperative factors: pain intensity, pain duration, immobilization and inactivity.

Risk factors for the development of CPOP are variable and may be individual and surgical. Most important factors are pain intensity and nervous injury. Other associated factors are: female gender and psychological factors (anxiety, depression, catastrofization, fear, passive behavior and secondary gain).

Age

Younger people run less risk of developing CPOP after thoracotomy^{18,19}, breast cancer³ and elective abdominal²⁰ surgery.

Genetic

It seems that changes in the GTP-cyclohydrolase gene, seen in approximately 15% of the population, is associated to protection against neuropathic pain and painful perception decrease. GTP-cyclohydrolase regulates tetrahydropypterin production, which is an essential co-factor for the production of catecholamines, serotonin and nitric oxide, modulators of neuropathic and inflammatory pain²¹. There is a family history report on hypertension with decreased pain perception, which may be associated to mitochondrial DNA²², factor still very controversial²³. Genetic polymorphism of catecholamine-O-methyltransferase gene is associated to the impact on pain perception and on the risk of developing CPOP²⁴.

Perioperative pain

Severe pain immediately after surgery is a significant risk factor for CPOP. There are evidences that acute pain treatment not only accelerates surgical recovery, but also decreases the risk for pain persistence²⁵. Acute post C-section pain is an independent risk factor for the development of CPOP²⁶. Pain after and before amputation is a significant predictor of chronic pain intensity, which suggests that the risk for post-amputation chronic pain is higher in individuals with higher pain scores in all those moments²⁷. Pain immediately before amputation influences the development of stump and phantom pain. However, a study has not associated acute pain to CPOP six months after total knee arthroplasty²⁸.

Psychosocial

Anxiety is a major factor for pain intensity. Anxious patients are in general hypersensitive to stimulation and psychologically more reactive. Depression is related to higher postoperative pain intensity, which makes us consider that the improvement of such symptoms and

of postoperative pain may interrupt pain chronicity process²⁰. Fear of surgical consequences in the long run was associated to more pain, worse global recovery and quality of life; however optimism was associated to better recovery and quality of life²⁹.

Surgical

Patients submitted to thoracotomy with different access pathways and closure techniques have evolved differently¹⁸. Surgical procedures lasting more than 3 hours are associated to increased risk for developing CPOP; however, longer surgeries are probably more complex and risky²⁹. Change in inguinal sensitivity one year after surgery depends on the surgical technique¹⁹. Different techniques for different procedures evolve in different ways to CPOP. Video thoracoscopy poses a lower risk as compared to conventional thoracoscopy. Risk is higher for breast cancer surgery with axillary exploration².

Prevention

Prevention can be obtained as follows:

- Less traumatic surgery;
- Avoid nervous injury;
- Diabetes *mellitus* control;
- Preoperative analgesia;
- Perioperative analgesia;
- Postoperative analgesia;
- Early mobilization;
- Improvement of venous return;
- Avoid compressing structures.

Early and late postoperative pain prevention is a major challenge for anesthesiologists and surgeons, since it is difficult to treat CPOP. In an attempt to improve its perioperative control and to estimate postoperative pain, more and more studies are being developed every day to implement effective measures and to minimize unnecessary and inadequate surgeries³. Postoperative pain is where the physician may influence the most³.

CPOP prevention should be performed not only by the anesthesiologist, but also by surgical teams. Patients submitted to surgical procedures should be aware of the risk of developing CPOP, since its incidence is high. Each elective surgical procedure should be carefully evaluated, analyzing benefits and risks. The surgical team shall know the different surgical techniques to which patients may be submitted, being able to choose, when possible, the technique exposing patients to the lowest risk of de-

veloping CPOP. Carefully dissection of the surgical field avoiding nervous injuries and decreasing local inflammatory process and less invasive techniques may be strategies to prevent pain¹⁰.

A probability scale of the risk for developing CPOP was developed mentioning as some predictors age, gender, preoperative pain, type of surgery, incision size and level of anxiety, among others. It was validated for inpatients and outpatients and has good correlation with the development of acute postoperative pain³⁰. Since the presence of acute postoperative pain is associated to the risk of developing chronic pain, if we identify potential risk patients, more and more preventive measures, such as adequate and intensive treatment of pain throughout the perioperative period, may be performed to block CPOP development.

Treatment of pain

Treatment may be achieved with drugs, physical measures and blocks¹⁷. Drugs used are: anti-inflammatory drugs, paracetamol, dipirone, opioids, anticonvulsants, antidepressants, neuromuscular blocker, clonidine, ketamine and lidocaine. Several blocks may be performed by epidural, intra-articular, in plexus, nerve or infiltration drug injection. Physical measures include: mobilization, kinesiotherapy, desensitization, active movements and orthosis.

Preventive analgesia may be induced, which is the treatment started before surgery to prevent physical consequences of nociceptive transmission to central neuroplasticity. Similar treatment, when used before surgery has potential to be more effective than after the beginning of incision (preemptive analgesia)³¹.

Gabapentin and pregabalin are substances analog to GABA (gamma-aminobutyric acid) neurotransmitter, but do not bind to gabaergic receptors. Gabapentinoids bind to a sub-unit of voltage-dependent calcium channels of pre-synaptic neurons causing changes in the conformation with inhibition of abnormal neuronal activity, decreasing glutamate, norepinephrine, P substance and other neurotransmitters release, changing the neuroplasticity cascade. The prophylactic use of pregabalin decreases protein expression of calcium channel in the spinal cord, which is correlated to increased nociception and allodynia³². Gabapentin in single dose one hour before surgical procedure (herniorrhaphy and hysterectomy), decreased the risk and intensity of chronic pain in a 6-month follow-up^{33,34}. It has also been observed that ketamine³⁴ and gabapentin decreased postoperative opioid consumption^{33,35}. A

study with rats has shown that perineural lidocaine infiltration decreased neuropathic pain after sciatic nerve compression³⁶.

A study evaluating three analgesic methods for patients submitted to thoracotomy has observed that patients with preoperative epidural block with bupivacaine and morphine presented less pain six months later as compared to patients with epidural block analgesia after the procedure and those with venous morphine analgesia³⁷.

A metanalysis including randomized double-blind clinical trials of several surgical procedures about preemptive analgesia and evaluating acute and chronic pain has observed that the use of venous non-hormonal opioid anti-inflammatory drugs and N-Methyl-D-Aspartate receptors antagonists did not show preemptive effects³⁸.

It seems that multimodal analgesia with the association of drugs and techniques is more adequate to treat pain and decreases side effects. It should be done preventively and with enough duration to prevent central sensitization by previous pain, surgical trauma and by postoperative inflammation. However, adequate studies are needed for a better evaluation of chronic postoperative pain syndromes.

CONCLUSION

Chronic postoperative pain is a morbidity of high incidence and affects quality of life of patients, although very often it is neglected by the medical team. CPOP is difficult to treat being prevention the most effective measure. With a better understanding of pathophysiological bases for postoperative pain perpetuation and of risk factors, new options to treat pain are appearing. The real benefits of preventive drugs are being increasingly studied. To prevent pain, surgical teams and patients should be aware of the risks of each procedure, not only in the immediate postoperative period, but also in the long run.

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