Chapter

Abdominal Hernia Pain: Chronification Mechanisms after Hernia Surgery

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Abstract

Groin pain is the most common cause of surgical intervention. There are 3 parameters that increase the chances of chronic pain. On the one hand, starting the surgery with high intensity pain that has not been previously controlled. On the other, insufficient anesthetic and analgesic control during the surgical procedure. Finally, an inadequate management of acute postoperative pain. The presence of groin pain and its poor control before the intervention predisposes to difficulties during the perioperative process. Thus, the appearance of acute postoperative pain not adequately controlled will prevent its remission in a natural way in the usual period (approximately 1 month) and will cause it to progress in intensity and continuity (from 1 month to 3 months after surgery), transforming into a chronic pain (from 3 months after the intervention). In this process of chronification, in which pain goes from nociceptive to neuropathic, different physiological sensitization mechanisms are involved, both peripheral and central. The chronification of the painful process and, ultimately, the therapeutic approach that we will have to use to try to prevent this process depends to a large extent on these modifications that facilitate the change in the nature of pain.

Keywords: groin pain, acute postsurgical pain, chronic postsurgical pain, sensitization

1. Introduction

1.1 Origin of groin pain

It refers to the discomfort that occurs in the groin area of abdominal wall. The most common causes of groin pain include:

- Pulling on a muscle, tendon, or ligament in the leg
- Hernia
- Hip joint disease or injury

Less common causes include:

- Inflammation of the testicle or epididymis and related structures

- Torsion of the spermatic cord attached to the testicle (testicular torsion)
- Tumor of the testicle
- Kidney stones
- Inflammation of the large and small intestine
- Skin infection
- Swelling of the lymph nodes
- Urinary infection

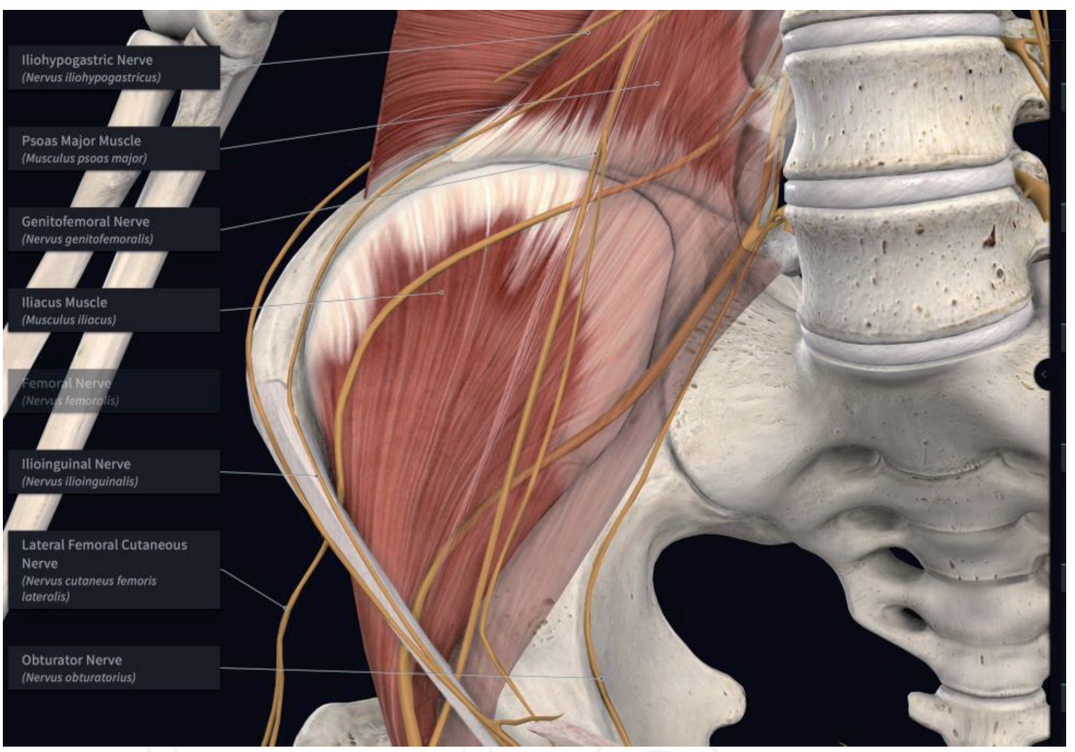

Figure 1.
Nervous system in the groin hernia area (3D 4Medical app).

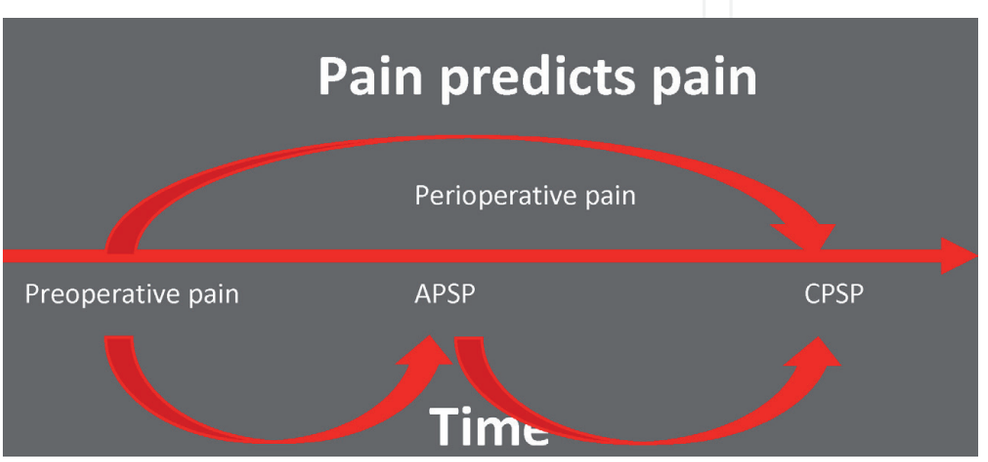

Figure 2.
Predictability of the appearance of CPSP.

This groin pain is perceived, integrated, transmitted and evaluated by neurons and the nervous system, but we have not yet elucidated how this process takes place. Such is the profuse network of nerves that cover the area, that their involvement is a not uncommon phenomenon (**Figure 1**).

In fact, the most frequent surgical reason is inguinal pain resistant to conservative treatments. Besides, poor preoperative pain control is a key factor in developing acute and chronic postsurgical pain (CPSP; **Figure 2**).

2. Risk factors

Each patient who develops CPSP has a specific genotype, medical history, previous experiences, beliefs and psychosocial conditions related to their pain; but, in general, there are some common risk factors in the development of chronic pain.

- ***Psychosocial factors***: Anxiety, depression and catastrophizing that surround the patient during the perioperative period.

- ***Demographic factors***: In some surgeries, age is a determining factor (i.e. young women for mastectomies [1]). In others, the male gender is more prone than the female [2, 3].

- ***Genetic factors***: Several authors point to the relationship of different clinical pathologies such as fibromyalgia, migraine, irritable bowel, irritable bladder, Raynaud's syndrome … as markers of chronic postsurgical pain [4, 5].

- ***Preoperative pain***: The presence of preoperative pain has been correlated in different studies with the development of CPSP. Of all the types of surgical interventions, the hernia procedure stands out for its high preoperative pain rates [6–9].

- ***Surgical factors***: Some important surgical factors may be related to the development of CPSP such as:

  ○ Duration of the operation (more than 3 h),

  ○ Surgical technique (laparoscopy vs. open),

  ○ Incision (site and type),

  ○ Experience of the surgeon,

  ○ Center where the intervention is carried out [10].

- ***Acute postsurgical pain (APSP)***: Various studies show the importance of optimal APSP control to avoid chronification of postsurgical pain. Among them, surgeries such as groin, breast, hip, knee … are the most identified [11–13].

However, and despite the fact that there are different studies addressing this issue, the controversy remains dominant. To date, it can only be suggested that they do not play in favor of a better recovery or a lower probability of chronification, in addition to reducing quality of life in the process; but in no case can we establish a universally accepted causal relationship [3, 13–16].

3. Nociception

For the response to a noxious stimulus (be it chemical, thermal, pressure or any other characteristic that can cause pain), there are structures sensitive to those stimuli in the periphery: they are nociceptors [17].

Different classes of afferent nerve fibers are responsible for the communication of nociceptive information and pain:

a. **Type Aβ**: with a myelin sheath, are sensitive fibers responsible for touch and pressure.

b. **Type Aδ**: with a myelin sheath are responsible for the transmission of localized acute pain, temperature and part of the touch.

c. **C fibers**, without myelin sheath are responsible for the transmission of deep diffuse pain, smell, information from some mechanoreceptors, responses of the reflex and postganglionic arcs of the autonomic nervous system.

In a basal state, a noxious stimulus depolarizes a sensory or nociceptor neuron. The stimulation of nociceptors causes the propagation of the nerve stimulus to the dorsal horn of the spinal cord. Control at the spinal level is carried out in the gelatinous substance of Rolando (Rexed plate II) by stimulating inhibitory interneurons (Golgi II type) that cancel or reduce the nociceptive signal towards the lateral spinothalamic tract. In addition, glutamate is released, an excitatory amino acid that binds to a specific receptor, called AMPA and located in a postsynaptic neuron that transmits information to the higher centers of the CNS. Different brain centers are stimulated from the thalamus:

I. ***Periaqueductal gray substance (PAGS):*** Located in the midbrain, it is one of the most important nuclei and its functions are mediated by the opioid system. Its activation allows the inhibition of the painful process. It is connected with brain structures, with the ascending bundles and sends its projections to structures of the pons such as the nuclei of the raphe magnum.

II. ***Nuclei of the raphe magno***: Located in the protuberance, receives connections from the ascending systems and the PAGS. It sends its axons to the first afferent synapse of the posterior horn and its nature is serotonergic.

III. ***Cerulean nucleus***: Located on both sides of the fourth ventricle in the bridge. It is noradrenergic in nature.

The prefrontal cortex integrates all the information and the patient feels pain [18]. From these same superior nuclei, descending pathways are set in motion and reach the dorsal horn of the medulla again releasing endogenous inhibitory substances (mainly opioids and GABA). These inhibitory substances act by modulating the transmission of the stimulus: on the one hand, by decreasing the release of glutamate, and on the other, by hyperpolarizing the membrane of the postsynaptic neuron [19]. Inhibitory interneurons also come into play, which by releasing endogenous opioids, mimic and potentiate the inhibitory effect of the descending pathways.

3.1 Nociceptive pain

Refers to pain that is associated with actual or threatened damage to non-neural tissue and involves the activation of peripheral nociceptors (IASP Taxonomy, 2015). There are three major forms of nociceptive pain:

3.1.1 Somatic

Includes all pain originating from non-visceral structures, (i.e. skull, meninges, and teeth) and is the most common cause of consultation for almost all specialties, especially those dedicated to the locomotor system.

3.1.2 Myofascial

Extremely frequent, although in many cases it is not diagnosed as such. It is a neuromuscular dysfunction with a tendency to chronicity. It consists of a regional pain disorder, which affects the muscles and fasciae, so that the muscles involved have trigger points as essential components. In addition, regional and segmental autonomous alterations may coexist.

3.1.3 Visceral

Dull, diffuse and poorly localized pain, referred to an area of the body surface, being frequently accompanied by an intense motor and autonomic (sympathetic) reflex response. The stimuli that can produce visceral pain are: spasm of the smooth muscle (hollow viscera), distension and ischemia.

4. Neuropathy

Sometimes there is no relationship between the painful stimulus and the response that it originates in the CNS: it is then when a very important amplification of the nociceptive signal occurs, and this phenomenon is known as neuronal sensitization or neuropathy, so that the information transmitted to the brain causes a disproportionate pain reaction. This derangement occurs both at the peripheral and central levels.

4.1 Neuropathic pain

Persistent pain becomes a pathological state that includes a series of elements that facilitate its generation and persistence over time. For this reason, any process that injures nerve tissues or causes neuronal dysfunction can produce neuropathic pain (NP). NP is qualitatively characterized by the absence of a causal relationship between injury and pain. Its etiology is very diverse and the relationship between etiology, pathophysiological mechanisms and symptoms is complex. NP differs from nociceptive pain in several aspects (**Table 1**).

The balance between arousal and inhibition of the somatosensory system is dynamic and is influenced by context, behaviors, emotions, expectations, and pathology. In NP this equilibrium is broken and a loss in inhibitory currents has been demonstrated, with dysfunction in the mechanisms of production and release of GABA, a decrease in μ-opioid receptors in the dorsal root ganglia, and less receptivity to opioids in the spinal neurons. In summary, the neuronal pathological

	Nociceptive (somatic / visceral)	Neuropathic
Official definition	Pain caused by activation of peripheral / visceral nociceptors	Pain caused by PNS / CNS dysfunction
Mechanism	Natural physiological transduction (nociceptor)	Ectopic pulse generation
Symptom location	Local pain + referred	Territory of innervation of the affected nerve pathway
	No neurological topography	
Quality of symptoms	Common painful sensations of daily life - easy verbal description (i.e. Head ache, belly ache...)	New, unfamiliar, aberrant sensations: difficult verbal description (i.e. burning, electrical...)
	Normal neurological examination: response and aggression correspond	Hypo / hypersensitivity: response and aggression do not correspond
Treatment	Effective: conventional analgesia	Partially effective: antiepileptics, antidepressants

Adapted from Serra Catafau, Treatise on neuropathic pain (Adapted from SGADOR Handbook).

Table 1.
Differences between nociceptive and neuropathic pain.

process changes in the course of injury and its pathophysiological mechanisms are evolutionary. The mechanisms that trigger NP produce:

- Local inflammation
- Glia cell activation
- Changes in neuronal plasticity of nociceptive pain-transmitting pathways

5. Acute pain

Acute pain is an experience, usually of sudden onset, of short duration in time and with remission parallel to the cause that produces it. There is a close temporal and causal relationship with tissue injury or nociceptive stimulation caused by disease. Its duration ranges from a few minutes to several weeks. Acute pain has been attributed a "protective" function, its presence acts by preventing the individual from developing behaviors that may increase the injury or leads him to adopt those that minimize or reduce its impact. The fundamental emotional response is anxiety, with less involvement of other psychological components. Its characteristics offer important help in establishing the etiological diagnosis and selecting the most appropriate treatment. Its presence follows a classic treatment scheme such as Pain-Symptom. The most common causes of acute pain are:

1. Visceral pain
    i. Gastrointestinal
    ii. Biliary
    iii. Urological
    iv. Cardiovascular

v. Pulmonary

vi. Nervous system

vii. Pancreatic

viii. Gynecological

2. Muscle Skeletal Pain

i. Arthropathies

ii. Chest wall pain

iii. Fractures

iv. Costochondritis

v. Tendinitis

3. Oral pain

4. Burn pain

5. Postoperative pain

6. Chronic pain

Chronic pain extends beyond the tissue injury or organic involvement with which, initially, there was a relationship. It can also be related to the persistence and repetition of episodes of acute pain, with the progression of the disease, with the appearance of complications thereof and with degenerative changes in bone and

	Acute Pain	**Chronic pain**
Purpose	Initial-biological	Initial-destructive
Duration	Temporary	Persistent
Generator mechanism	Unifactorial	Multifactorial
Affected component	Organic+++Psychic+	Organic+Psychic+++
Organic response	Adrenergic: raise in heart rate, arterial hypertension, sweating, pupillary dilation	Vegetative: anorexy, constipation, less lybid, insomnia
Affective component	Anxiety	Depression
Physical exhaustion	No	Yes
Therapeutic goal	Cure	Relief and adaptation

Table 2.
Differences between acute and chronic pain.

musculoskeletal structures. Examples of this are cancer, secondary pathological fractures, osteoarthritis, postherpetic neuralgia, etc.

Chronic pain does not prevent or avoid damage to the body. Both their nature and their intensity show great variability over time, in many cases the complaints are perceived as disproportionate to the underlying disease. The most frequent repercussions in the psychological sphere involve anxiety, anger, fear, frustration or depression, which, in turn, contribute to further increasing pain perception. The socio-family, labor and economic repercussions are multiple and generate important changes in the lives of the people who suffer from it and their families: disability and dependency. The need to use drugs to relieve pain becomes a potential risk factor for use, abuse and self-prescription, not only of analgesics, but also tranquilizers, antidepressants and other drugs.

In its management, in addition to the physical aspects of pain, the other components, emotional, affective, behavioral and social, must be taken into account. The treatment scheme is complicated, we are facing the Pain-Syndrome (**Table 2**).

7. Postsurgical groin pain

7.1 Acute postsurgical groin pain

All surgical intervention is associated with acute postsurgical pain (APSP) whose intensity decreases during the first days and weeks, in parallel with the tissue repair process. However, sometimes this pain lasts longer than is reasonable in relation to the surgical procedure. This fact can lead to the appearance of severe and disabling chronic pain syndromes, frequently associated with certain surgical procedures.

The definition of chronic postoperative pain (CPSP) does not find a consensus among the different authors in the literature reviewed. The most commonly used definition continues to be that of McRae [20, 21] based on the following aspects:

a. pain with a minimum duration of two months after a surgical procedure

b. after excluding other etiologies of pain

c. ruled out any pre-existing cause of pain (**Figure 3**).

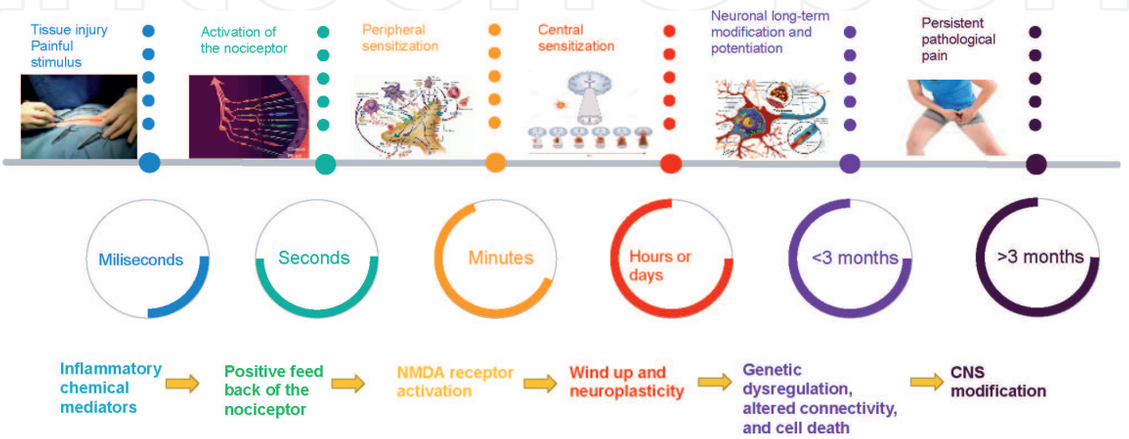

Figure 3.
Temporal evolution of postsurgical pain (adapted from Woolf and salter, science 2000; 288: 1765 [22]).

CPSP originates from the injury to the nerves and tissues inherent in the surgical process. During the immediate postsurgical period appears the breakthrough pain limited to the surgical site and its vicinity and develops through the direct activation of nociceptors, the inflammatory process and, in some cases, of direct nerve injury [23]. For this reason, the patient will present pain in the area of the surgical scar (primary hyperalgesia) and around it (secondary hyperalgesia). These changes are usually reversible and the normal sensitivity of the nociceptive system will then be restored. This type of pain, APSP, has a known beginning and an end in direct relation to tissue repair. In addition, it responds effectively to non-steroidal anti-inflammatory drugs, paracetamol, and minor or major opioids.

In the event of nerve injury during surgery, the neuropathic component of pain can immediately develop and persist in the absence of any noxious peripheral stimuli or ongoing peripheral inflammation [24]. The prerequisite for the development of CPSP is an injury to the major nerves that run through the surgical site. However, in a small group of patients, an ongoing inflammatory response may help maintain inflammatory pain and lead to a CPSP, such as that occurs after inguinal mesh hernia repair [25]. During progression from APSP to CPSP after inguinal hernia surgery:

- 7% of patients present severe acute pain the first 24 h;
- 14% of patients present subacute pain that could last until 8 weeks after surgery;
- 12% of patients present CPSP that could last until 12 months after surgery (80% of whom present Neuropathic component)

The incidence of chronic pain after inguinal hernia surgery rates from 5–63%, with an estimated incidence of severe chronic pain (VAS > 4) between 2% and 4%.

7.2 Inguinal chronic pain

Inguinal hernia surgery can trigger a post-herniorrhaphy chronic inguinal pain syndrome, which can occur in up to 10% of the interventions performed [21].

The symptoms of postherniorrhaphy neuropathic inguinodynia consist of pain, paresthesias, allodynia (sensation of pain in the presence of non-harmful stimuli such as touch or pressure), pain radiating to the scrotal area, labia majora of the vagina and Scarpa's triangle. This symptomatology also worsens with walking or hyperextension of the hip and decreases with decubitus and flexion of the thigh. These last aspects of the symptomatology make us see that the affectation of the nervous tract is the main actor of the chronic pain postherniorrhaphy [26].

There are three types of causes for the appearance of this painful syndrome:

i. Non-neuropathic

   a. Reaction of the periosteum of the pubis

   b. Keloid scar formation

   c. Direct pressure exerted by bent or wrinkled prosthetic material (mesh) [27].

ii. Neuropathic

a. Fibrosis of the perineurium of the nerves that run along the inguinal path (ilioinguinal nerve and genital branch of the genitofemoral nerve)

b. Compression of these by suture material, staples or prosthetic material

iii. ***Direct injury to the nervous tract in a complete or incomplete manner***. It can be produced by traction, direct cutting with a scalpel, or excessive thermocoagulation.

7.2.1 Peripheral sensitization

Peripheral sensitization involves lowering the discharge threshold from the peripheral terminal of the nociceptor. The molecules released in response to tissue damage and the activation of cells in the environment such as keratinocytes, mast cells, lymphocytes, platelets or the nociceptor itself, are called inflammatory soup (Substance P, calcitonin gene receptor protein [CGRP], quinines, amines, prostaglandins, growth factors, chemokines, cytokines, ATP, protons, etc.). These molecules induce morphological and functional changes in the neuron, which consequently generate an increase in the expression of structures such as the Na^{2+} channels and transient receptor potential cation channel subfamily V member 1 [TRPV1]; or molecules such as neuropeptides, or brain-derived neurotrophic factor [BDNF]. The interaction of these molecules with the different membrane receptors initiates an activation cascade of intracellular second messengers that modify the firing capacity of the cell, the final consequence being a greater capacity to respond to stimuli. This circumstance translates clinically into the following processes: hyperalgesia, allodynia, and spontaneous pain.

Spontaneous pain can be caused by:

i. An abnormal response to stimuli that normally do not cause harm (arterial heartbeat, increased temperature)

ii. Ectopic discharges from the damaged nociceptor itself

iii. Those produced by surrounding healthy fibers in response to the release of TNFα by damaged Schwann cells

At present, it is proposed a new state of the nociceptor, called "priming", in which, a sensitized nociceptor, after a few hours will have a normal response to physiological stimuli, but will have an increased response to stimuli derived from inflammation. This state lasts for weeks and the hyperalgesic response to inflammatory agents is greater, which could be a possible explanation for the maintenance of chronic pain.

In a situation in which nociceptive information continues to be sent from the periphery to the dorsal horn of the spinal cord, the nociceptive neuron itself sends, from its soma (without the need for external stimulation) substance P and peptide related to the calcitonin gene (PRCG). These substances bind to neutrophils, mast cells and basophils, and release pro-inflammatory molecules: cytosines, bradykinins, histamines, cyclooxygenases, prostaglandins, eicosanoids and nerve growth factor (NGF). All this "inflammatory soup" produces changes in pH, release of ATP from injured cells, synthesis and release of nitric oxide (NO), etc., which induces amplification of the signal towards the spinal cord and higher centers and causes

what is known as peripheral sensitization, which contributes in a very important manner to the maintenance of chronic pain.

7.2.2 Central sensitization

If the nociceptive impulses are of great intensity or are sustained over time, plastic changes occur in the neurons of the posterior horn that facilitate the transmission of the nociceptive impulse. These changes in functionality are called central sensitization and cause specific clinical manifestations. It may represent the anatomical and physiological substrate to the fact of persistence of pain in the absence of peripheral nociceptive impulses in chronic pain, since the state of hyper-reactivity of the system would allow to explain the autonomous activity of the system in the absence of peripheral stimulus. In general terms, the following changes can be considered, which can all occur simultaneously or simply manifest some of them:

I. Disinhibition of the N-methyl-D-aspartate (NMDA) receptor by release of the Mg^{2+} ion at the first medullary synapse

II. Access of peripheral Aβ fibers to the nociceptive system. It is one of the causes of the phenomenon of allodynia

III. Dysregulation of the GABAergic system of inhibitory interneurons, which finally produces an alteration in the current of the Cl^- channel.

IV. Activation of the glia with the release of pro-analgesic substances

V. Alteration of the regulatory capacity of the downstream system

There is also the release of glutamate, which binds to specific receptors, which are not expressed in situations of acute pain. When activated, they contribute not only to depolarize the postsynaptic neuron, but also to generate a series of intracellular changes, which will increase the nociceptive signal. In response to peripheral sensitization, the primary afferent pathways also release substance P, resulting in an increase in signal. In situations of chronic pain there is also a reorganization of the neuronal structure: axonal collateral branches appear that increase the amount of nociceptive afferent signal.

On the other hand, a loss of efficacy of the inhibition produced by the descending pathways has been described, with a decrease in the release of endogenous opioids, and even cellular degeneration of those descending neurons, which indirectly also increases the nociceptive signal that is send to higher centers.

All these changes greatly amplify and sustain the nociceptive signal produced in the dorsal horn of the spinal cord, producing what is known as central sensitization.

The main clinical manifestations of nervous sensitization are hyperalgesia and allodynia phenomena, with the consequent increase in the extension of the painful area.

The presence of sensitization leads to the appearance of vicious circles in which there is a continuous sending of the afferent signal from the periphery to the brain centers in the absence of stimuli that generate them. This sustained stimulation leads to adaptive changes in the brain, such that the brain remains active even in the absence of noxious peripheral stimulus.

This continuous brain overexcitation conditions the effectiveness of the integrative pain response of the higher centers and the inhibitory descending pathway, in such a way that there is no inhibition proportional to the ascending amplified stimulus and the pain becomes chronic. This "centralizing" effect of the neuronal sensitization of nociceptors is one of the most relevant chronifying factors in the postoperative period of surgeries that present moderate to severe acute pain, that is not adequately controlled.

7.2.3 Pharmacological strategies

The type of pain, its location, duration and intensity determine the pharmacological approach (**Figure 4**).

- **Drugs that target peripheral sensitization**: such as topical **capsaicin** (i.e. 8% capsaicin patch); topical lidocaine (i.e. 5% lidocaine patch); NSAIDs; paracetamol and local anesthetics.

- **Drugs that target central sensitization:** such as serotonin reuptake inhibitors (SSRIs); tapentadol; tramadol; opioids; calcium channel ligands; adjuvants; tricyclic antidepressants; anticonvulsants and COX-2.

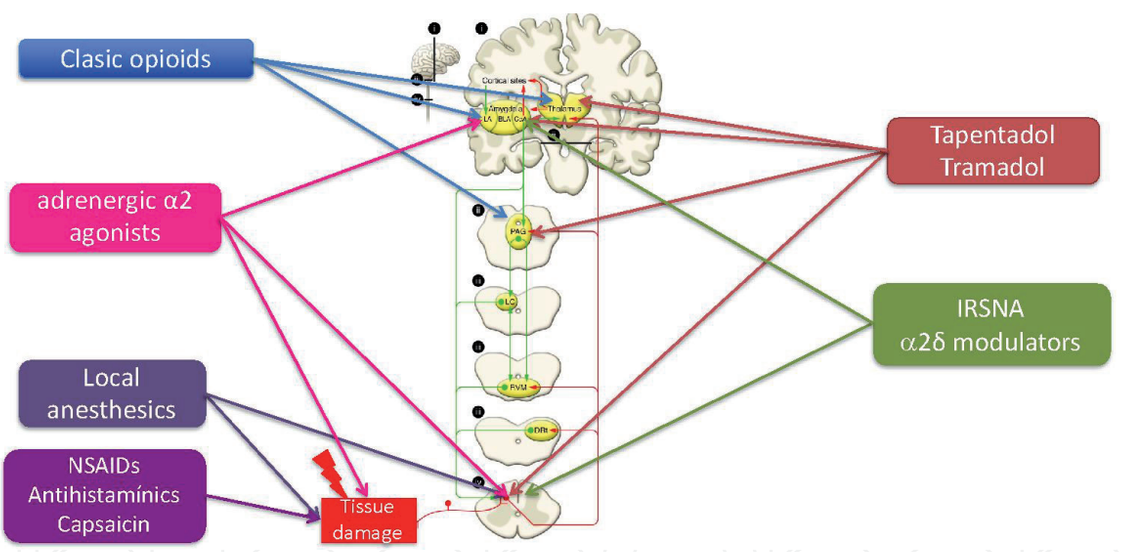

Figure 4.
Pharmacological approach to chronic pain.

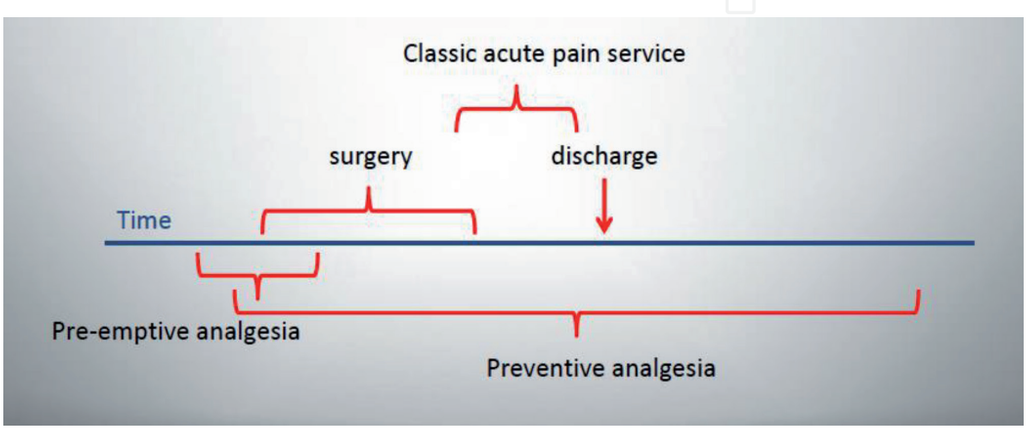

Figure 5.
Perioperative analgesia.

7.2.4 Preventive strategies

Blocking the pain signal before it reaches the central nervous system prior to surgery will prevent the development of central sensitization. The times that include the first consultation, the referral to the specialist, the decision of surgical treatment, the pre-anesthetic consultation and the appointment for surgery would favor peripheral and central sensitization if pain is not controlled, making the pain chronic and making it independent of the injury.

7.2.5 Rescue strategies

Using aggressive perioperative analgesia (antihyperalgesics, regional blocks, and multimodal analgesia) during the peri-surgical period could reduce the incidence of CPSP (**Figure 5**).

7.2.6 Are all the operations necessary or appropriate?

Chronic pain is common after hernia surgery. Patients with pain before the operation benefit from surgery, but some patients who have no pain before hernia repair surgery develop significant groin pain later. Watchful waiting has proven to be safe [28] and profitable [29] in patients with asymptomatic inguinal hernia. It is a theme of debate whether surgery is appropriate in asymptomatic hernias and possibly in some other interventions as well.

8. Summary

CPSP is a common entity in interventional procedures today. Progress continues in the standardization of prevention and treatment strategies for this delicate problem in the technical and organizational sphere.

The improvement efforts aim to:

- Early identification of patients with preoperative pain who need intervention.
- Avoid delaying this intervention as far as possible, and if there is a delay, provide adequate pain management until the time of surgery.
- At the time of the intervention, determine the least invasive and most appropriate surgical technique for the pathology.
- Implement the most appropriate perioperative anesthetic and analgesic techniques for the patient.
- Once intervened, individualize postoperative analgesia so that APSP is as low as possible, thus avoiding, as far as possible, chronic pain.

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Conflict of interest

I declare that I have no conflict of interests.

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