New Concepts in Acute Pain Management: Strategies to Prevent Chronic Postsurgical Pain, Opioid-Induced Hyperalgesia, and Outcome Measures

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Chronic postsurgical pain (CPSP) is a pain syndrome that has attracted attention for more than 10 years. The criteria for this diagnostic entity were established by the International Association for the Study of Pain (IASP) in 1999. CPSP is a pain syndrome that develops postoperatively and lasts for at least 2 months in the absence of other causes for pain (eg, recurrence of malignancy, chronic infection, and so forth). Pain continuing from a preexisting disease is not considered as CPSP.[1] In this article, the authors discuss the etiopathogenesis of CPSP and interventions that can help prevent and treat this condition.

The following case report illustrates the particular clinical presentation of CPSP.

A 48-year-old active businesswoman was scheduled for a Nissen fundoplication by an open thoracic (Belsey) approach. This surgical intervention was indicated because of acid reflux symptoms resistant to antireflux medications. The type of surgery was chosen based on the demonstration of a Barrett esophagus by the radiological examination. The patient was obese with a body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared)

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of 30 and had quit smoking 10 years prior to surgery and thus was documented to be of the American Society of Anesthesiologists physical status 2. The procedure was done under general anesthesia combined with a thoracic epidural analgesia. Postoperative pain was managed using patient-controlled thoracic epidural analgesia (PCEA) with a bupivacaine-sufentanil mixture and intravenous proparacetamol until the fifth postoperative day. During the following days, proparacetamol and tramadol replaced the PCEA. The postoperative course was uneventful. The patient was discharged home on the eleventh postoperative day.

Six months later, this patient was readmitted for a partial costal resection for unbearable right thoracic pain at the old thoracotomy site. This procedure was ineffective to relieve the pain, and the patient was thus referred to the pain clinic. Multiple attempts with escalating analgesic medications and local infiltrations were performed with only modest results. The patient finally benefited from a spinal cord stimulator but could not return to work because of pain.

During the initial 6 months after her thoracotomy, the patient consulted the surgeon 3 times and the general practitioner more than 10 times, who referred her to 2 different neurologists and 1 psychiatrist. However, the patient never consulted an anesthetist or a chronic pain physician!

A few important lessons can be drawn form this case report.

In most cases of CPSP, the primary anesthetist providing the initial anesthesia to the patient is not aware of the occurrence of CPSP because this syndrome develops when the patient is already back home.

Further, in some patients, CPSP diminishes or resolves over time, whereas for some (0.5%–1.5% of all the patients undergoing surgery) it becomes an invalidating chronic pain necessitating frequent visits to chronic pain facilities.[2] Therefore, prevention is of critical importance.

Before discussing the strategies to prevent CPSP, some facts about CPSP are mentioned.

WHAT IS THE INCIDENCE OF CPSP

CPSP occurs in 10% to 50% of individuals after common operations, such as groin hernia repair, breast and thoracic surgery, leg amputation, orthopedic procedures (donor site pain, complex regional pain syndrome), and coronary artery bypass surgery (**Box 1**).[3] More worrisome, however, is the fact that 2% to 10% of these patients evolve toward developing severe chronic pain. The high number of patients undergoing surgery per year makes CPSP a potentially significant problem of public health. This fact, however, deserves several comments.

The data supporting the incidence of CPSP are estimations extrapolated mostly from retrospective evaluations.[3] In these series, it is not easy to make a clear-cut distinction between preexisting and postoperative persisting pains. Patients, questioned postoperatively, often do not accurately remember if the pain was present before or after surgery and for how long the pain had lasted. Consequently, an overvaluation of the real incidence of the phenomenon cannot be totally ruled out. Moreover, in the few prospective studies available in the literature (most including a small number of patients), the incidence of CPSP is lower than that reported in the retrospective ones.[4–6] For this reason, there is clearly a need for large prospective evaluations based on the exact definition of CPSP according to the IASP.[1]

Nevertheless, even if the exact incidence of CPSP is unknown, this problem is of critical importance when considering surveys of patients consulting chronic pain facilities. These facilities reveal that for a large fraction of patients (30% according to Crombie and colleagues[7]), the start of the pain syndrome was consecutive to surgery.

Box 1
Incidence of CPSP after various interventions

• Limb amputation: 60%–80%

• Total hip arthroplasty: 30%

• Hysterectomy: 5%–30%

• Caesarean section: 10%

• Breast surgery 20%–50%

• Groin hernia surgery: 10%

• Sternotomy: 20%

• Thoracotomy: 25%–60%

Data from Perkins FM, Kelhet H. Chronic pain as an outcome from surgery. A review of predictive factors. Anesthesiology 2000;93:1123–33.

This high incidence of CPSP is probably not a real surprise. The high incidence may be related to the ever-increasing incidence of diseases associated with proinflammatory states, such as asthma, inflammatory bowel diseases, or fibromyalgia, in developed countries. Asthma for example was rare in 1900. At present, asthma affects 15 million people in the United States.[8] One explanation could be that the population evolves toward a greater vulnerability to proinflammatory processes, and CPSP is just one of these processes. Moreover, an ever-increasing part of the population is obese, and obesity is recognized as a proinflammatory condition.[9] Obesity is also recognized as a favoring factor for the development of CPSP (see later).

CPSP is a pain syndrome that potentially affects a large and probably an increasing number of surgical patients. CPSP occurs after not only extensive but also simple procedures. In patients with chronic pain, a history of surgery is frequently noted as the starting point of the pain problem. Large prospective studies are, however, mandatory to determine the exact incidence of CPSP and to isolate the epidemiologic predisposing factors. These large series should also include a reproducible quantification of the physical functioning and emotional well-being of the patients.

MECHANISMS UNDERLYING THE DEVELOPMENT OF CPSP

CPSP syndrome results probably from a dysfunction of the mechanisms underlying secondary hyperalgesia.[10] At present, the cause of this dysfunction is not known. It is clear that long-lasting noxious stimulations, inflammation, or damages to the neuronal tissues, which all occur to some extent after surgery, give rise to a neuronal hyperexcitability that is mostly relatively short lasting and associated with reversible plastic changes in neuronal connectivity. In some circumstances, such as intense noxious stimulation, proinflammatory context, vulnerable patients, as well as persistent and more profound changes in transmitters, receptors, and ion channels, neuronal connectivity occurs, leading to irreversible plastic changes and CPSP. However, why some patients develop CPSP and others do not is still an unresolved question.

Pain has an important physiologic role, being a sensory modality that normally serves an adaptive function. Pain is a sensory warning system that activates protective reflexes and determines brain adaptive behaviors. Pain, as any sensory modality,

implicates both perception (something happens) and discrimination (what is happening now is different of the previous perception). Distinct physiologic mechanisms underlie these 2 functions. There are specific pain receptors (the nociceptors), and their perception can be significantly reduced (descending inhibitory controls) or amplified (primary and secondary hyperalgesia) at peripheral and central levels. This capacity to modulate pain perception is, in fact, the physiologic basis for discrimination. Unlike other sensory modalities, pain perception is strongly linked to the immune system (inflammatory reaction consecutive to tissue destruction). Pain can be powerfully amplified by activation of peripheral immune cells associated with peripheral nerves and by the activation of immunelike glial cells (microglia and astrocytes) within the central nervous system.[11]

Postoperative pain is a particular type of pain. This pain is definitively not to be considered as a simple symptom that disappears with wound healing or even as a symptom consecutive to an accidental trauma. Although most patients expect to experience pain after surgery, the pain in this setting can be exaggerated by psychological and pharmacologic factors. For example, the level of anxiety is known to correlate with the severity of pain from nociceptive stimuli. In addition, surgical tissue injury occurs during anesthesia, which may be important because anesthetic drugs interfere with sensory perception, but the effects of these drugs on pain processing are not necessarily unidirectional. For example, potent opioids produce both antinociception and hyperalgesia.[12] Halogenated vapors given to produce unconsciousness and amnesia also activate peripheral pronociceptive ionic channels, thereby augmenting neurogenic inflammation.[13]

Surgical trauma is associated with hyperalgesia (exacerbated pain in response to noxious stimulation) and allodynia (pain perceived to normally nonnoxious stimuli). Trauma leads to the release of inflammatory mediators at the site of injury, resulting in a reduction of pain threshold at the site of injury (primary hyperalgesia) and in the surrounding uninjured tissue (secondary hyperalgesia). Secondary hyperalgesia is the distinguishing mark of central sensitization, which is an activity-dependent increase in the excitability of spinal neurons (windup) as a result of persistent exposure to afferent input from peripheral neurons and inflammatory mediators. Prolonged central sensitization has the capacity to lead to permanent alterations in the central nervous system, including the disappearance of inhibitory interneurons, replacement with new afferent excitatory neurons, and establishment of new excitatory connections.[14] Central sensitization is not an abnormal but a modified perceptual response to a normal sensory input and results in the spread of sensitivity well beyond the peripheral site of injury (secondary hyperalgesia). Central sensitization is a modification of the homeostasis, leading to a new state necessary for healing. For example, hyperalgesia surrounding the wounded area promotes behavioral adaptation required for survival. It is also of critical importance to oppose the hypoalgesic influences induced by the trauma itself (stress induced or autoanalgesia). Hyperalgesia is part of the mechanism enabling discrimination in pain perception.

In the context of CPSP, secondary hyperalgesia has prompted attention for several reasons.

First, secondary hyperalgesia reflects transformations within the central nervous system, which share many features of mechanisms of memory. Both are dependent on the excitatory neurotransmission (glutaminergic neurotransmission). This particular type of transmission through the medium of N-methyl-D-aspartate (NMDA) receptors is involved in long-term modification of neuronal connectivity (neuroplasticity) and is demonstrated to play a key role in the induction and maintenance of central sensitization during physiologic and pathologic pain states.[15]

Second, secondary hyperalgesia is exemplary of the neuroimmune interactions in pain perception. Traumatic surgical injury to the peripheral nerve produces changes at the site of injury as well as in the dorsal root ganglia and dorsal horn of the spinal cord. Changes in dorsal horn involve neuronal and nonneuronal cells, begin within hours, and persist for up to months after surgery. Of particular interest are the changes involving nonneuronal tissues, such as the microglia (the resident macrophages of the brain and spinal cord). Recently, specific neuron-microglia-neuron signaling pathways have been elucidated. Microglia in the dorsal horn suppress neuronal inhibition by a sequence of steps (brain-derived neurotrophic factors), leading to an increase in intracellular chloride concentration in dorsal horn nociceptive output. Products released by activated microglia, including cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor α, are normally expressed in low concentrations in the spinal cord; however, this expression increases after peripheral nerve injury and peripheral inflammation.

These neuronal/immune interactions account for the symptoms of neuropathic pain associated with CPSP.[11] Dysfunctions of these mechanisms are suspected to induce a prolonged state of sensitization clinically manifested by CPSP.[10,16]

Clinically, patients developing CPSP presented a larger area of secondary hyperalgesia surrounding the surgical wound measured by the von Frey hairs than those not presenting with CPSP.[6,17–19]

The problem remains as to how and why physiologic posttraumatic hyperalgesia develop in pathologic hyperalgesia. One explanation could be the extent of surgery-associated neuronal damages. Nerve injury leads to abnormal plasticity resulting in ectopic pacemakerlike activity and nonphysiologic central sensitization. Nerve injury produces long-lasting central changes by potent immune tissue activation. This hypothesis is sustained by the fact that most of the time, the characteristics of CPSP are those of neuropathic pain.[20] Nevertheless, not all patients presenting with nerve damage consecutive to surgery develop CPSP,[21] and CPSP does not always or exclusively match the characteristics of neuropathic pain.[22]

Another explanation could be found in the preoperative antiinflammatory/proinflammatory status of the patient. In some patients, the proinflammatory response might be particularly intense or inadequate in regard to the surgical trauma. Arguments for this hypothesis exist. In developed countries, the incidence of obesity, which is a proinflammatory disease, is still increasing,[9] and CPSP occurs more frequently in obese patients. Moreover, in patients developing CPSP, a history of inflammatory process in the part of the body concerned by surgery is often noted.[18] This concept supports a kind of algesic proinflammatory priming favoring the development of the syndrome.[22]

Another circumstance related to the patient may also account for the development of CPSP. As previously noted, hyperalgesia is a physiologic process implicated in discrimination. Recently, a deregulation of the discrimination process was incriminated in the occurrence of some pathologies, such as fibromyalgia, in which patients show robust perceptual amplification of all the sensory modalities, including pain perception (the hypervigilance theory).[23] Patients with fibromyalgia share many common characteristics with those at risk of developing important acute postoperative pain and CPSP (female gender, anxiety, catastrophization, and so forth). Moreover, a history of trauma (including surgery) is frequently reported as a precipitating factor of the disease.[24] In this regard, CPSP may be part of these hypervigilant diseases unmasked in a vulnerable population by the preoperative stress and/or by surgery itself.

Circumstances linked to the anesthetic paradigm may help to turn physiologic into pathologic hyperalgesia. Large doses of synthetic opioids are administered during anesthesia, and it is now well recognized that opioids induce short-lasting analgesia

and long-lasting hyperalgesia. This effect is demonstrated in various animal models and numerous clinical settings, including the anesthetic paradigm.[25] This effect shares common mechanisms (excitatory neurotransmission) with trauma-induced hyperalgesia. In normal or nonanesthetic circumstances, this opiate-induced hyperalgesia is of critical importance to preserve homeostasis in stress conditions. Opioid contributes to maintaining the balance between hypoalgesic and hyperalgesic processes and between the proinflammatory and antiinflammatory mediators.[25] During surgery, the dose of opioids administered for anesthetic purposes is totally disproportionate in regard to the amount of endogenous opiates physiologically required. Consequently, in addition to trauma-induced hyperalgesia, patients are exposed to significant opioid-induced hyperalgesia. At present, there is, however, no direct demonstration that this opioid-induced hyperalgesia favors the development of CPSP.

CPSP is probably the result of a deregulation of the mechanisms underlying secondary hyperalgesia. Why this deregulation occurs is still under debate. The factors leading to this deregulation are probably related to the patients (proinflammatory vulnerability or pathologic discrimination process) and circumstances (procedures associated with neuronal damages or determining important inflammatory reactions, drug-induced hyperalgesia).

Because prevention is the cornerstone of the treatment of CPSP, it is therefore important to underline the patients and circumstances associated with the development of this syndrome.

WHO DEVELOPS CPSP
Risk Factors

The main risk factors are summarized in **Box 2**.

Because only a fraction of the surgical patients develop CPSP, it is important to detect these patients before surgery. Several predictive factors for CPSP have been identified, which are related to both surgery and patients.

Factors linked to surgery are obvious when considering the previous section. These factors include invasive procedures, redo interventions, long-lasting surgery, and surgery in a previously injured area.[26] Using an animal model for chronic postthoracotomy pain, Buvanendran and colleagues[27] showed that a 60-minute rib retraction produced an incidence of 50% of long-term allodynia. In contrast, a 5- or 30-minute rib retraction

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Box 2
Risk factors of developing CPSP

1. Type of surgery
2. Genetic predisposition
3. Female gender
4. Young age
5. Preoperative anxiety
6. Negative psychosocial factors
7. Obesity
8. Preexisting pain
9. Inflammatory state
10. Severe/poorly controlled postoperative pain

produced only an incidence of 10% of allodynia. In other words, all the surgical circumstances associated with important inflammatory reactions and damage to the nerve tissues are favoring factors.

Factors linked to the patients include the genetic background of the patient. It is well recognized that concerning pain perception and metabolism of analgesic drugs, the genetic polymorphism of the population is important. In this regard, there are some protective genotypes (homozygous carriers of a GTP cyclohydrolase I haplotype)[28] or phenotypes (children born of mothers with a familial history of hypertension, schizophrenia).[29,30] Nevertheless, according to the complexity of the mechanisms involved in pain perception, the recently isolated favorable haplotypes are not necessarily protective against all types of hyperalgesias (eg, somatic, visceral).[31] At present, the development of this area of study is still inadequate to allow systematic genotype screening to identify populations at risk of developing CPSP.

Gender: Female patients report greater level of pain after acute surgical procedures (moderate intensity of pain in 84% women vs 57% men). CPSP in female population occurs at a ratio greater than 2:1 when compared with men.[3]

Age: Young surgical patients are more prone to develop CPSP. Despite the fact that elderly patients have no significant modifications in pain thresholds and that peripheral neuropathies increase with aging, older age seems protective.[3]

Preoperative anxiety and/or catastrophization and negative psychosocial conditions: Preoperative anxiety has been identified to predispose to more intense postoperative pain during the first day after surgery.[32] High preoperative scores for anxiety, catastrophization personalities, and negative psychosocial situations are factors regularly reported in the history of patients suffering invalidating CPSP.[4,5,33]

Obesity: In the light of recent data, it is clear that the role of adipose tissue has changed from a lipid storage to an endocrine and immunoactive organ.[9] Modifications of the proinflammatory/antiinflammatory balance in obese patients favors the development of CPSP.[34,35]

The 3 following situations are also frequently found in the history of patients presenting with CPSP:

- Preexisting pain (not necessarily related to the surgical site)
- A history of an inflammatory process in the area of surgery[18]
- Conditions such as irritable bowel syndrome, migraine headache, fibromyalgia, and Raynaud disease.[36]

These situations are in accordance with the hypothesis of an algesic proinflammatory priming necessary for the development of CPSP.[22] In this regard, prospective studies would be interesting to confirm that neonatal surgery probably leads to increased pain sensitivity in later childhood and to residual pain.[37]

One of the most striking predictive factors of CPSP is the intensity of acute postoperative pain. Patients suffering intense postoperative pain are more prone than others to develop CPSP.[38–40]

In other words, the risk to intense acute postoperative is similar to that of CPSP.

STRATEGIES FOR PREVENTION

That the intensity of acute postoperative pain is a predictive factor for chronic pain is of critical importance for anesthetists. One of the first preventive measures is an adequate treatment of acute postoperative pain.

However, large surveys considering the efficacy of the treatment of acute postoperative pain revealed that the treatment remains inadequate. Dolin and colleagues,[41]

in a cohort of 20,000 patients from published data, reported that 41% of patients experience moderate to severe pain after surgery. These data are confirmed in a national survey done by Apfelbaum and colleagues.[42] These investigators demonstrated that 31% of patients had severe or extreme pain and another 47% had moderate pain after surgery.

How to Improve the Treatment of Acute Postoperative Pain to Prevent CPSP

Before surgery, it is important to detect patients likely to suffer intense postoperative pain. Patients do not equally face pain; there exists a large interindividual variability in pain sensitivity and response to analgesic medications. Sensitive patients deserve specific treatment. This distinction is also of critical importance to evaluate the efficacy of these specific treatments.

A simple way to detect these patients at the preoperative visit is to fulfill the Kalkman score, a validated risk scale based on patient's history and the type of surgery (**Box 3**).[43,44]

Other investigators have developed more sophisticated tools to detect at-risk patients. These investigators elaborated testing based on experimental pain. In this regard, psychophysical measures exploring static pain parameters (pain thresholds, magnitude estimation of suprathreshold nociceptive stimuli, and tolerance) have been regularly reported to predict the intensity of acute postoperative pain in the early phase of an injury.[45] Nevertheless, these measures of response to an acute, phasic, experimental stimulus are less indicative of the complex pain modulation process that occurs after surgery. Some aspects of such modulation can be quantified by using the dynamic psychophysical measures of temporal summation and evocation of diffuse noxious inhibitory control, a measure recently reported to predict the risk of CPSP after thoracotomy.[46] In contrast with the Kalkman score, these tests are time consuming and resource consuming and therefore not easy to perform in daily clinical practice.

Box 3
Preoperative prediction of severe postoperative pain according to Kalkman and colleagues[43]

- Sex: female, 1 point; male, 0 point
- Age: younger than 30 years, 2 points; 31 to 65 years, 1 point; older than 65 years, 0 point
- Pain before surgery at the site: none, 0 point; moderate, 2 points; sévère, 3 points
- Regular use of opioids, 1 point
- Regular use of anxiolytic antidepressants, 1 point (otherwise 0)
- Open surgery, 1 point (otherwise 0)
- Type of surgery: thoracic, 3 points; abdominal, 2 points; orthopedic, 1 point; other, 0 point
- Long-lasting procedures (>120 minutes), 1 point (otherwise 0)
- Obesity (BMI>30), 1 point (otherwise 0)
- High level of anxiety at the preoperative visit, 1 point (otherwise 0)

The risk-intense postoperative pain is important when the score is 4 out of 15.

Data from Kalkman CJ, Visser K, Moen J, et al. Preoperative prediction of severe postoperative pain. Pain 2003;105:415–23; and Janssen K, Kalkman CJ, Grobbee DE, et al. The risk of severe postoperative pain: modification and validation of a clinical prediction rule. Anesth Analg 2008;107:1330–9.

Once these sensitive patients are detected at the preoperative visit, the anesthetists may help these patients to prepare themselves for surgery and postoperative pain. One way is to assist the patient to face the psychological stress associated with the surgery and its consequences. It is already mentioned that preoperative anxiety plays an important role in the intensity of postoperative pain, and anxious/catastrophizing personalities are factors recognized to favor CPSP.[32] Techniques to alleviate these negative mental statuses, such as autohypnotic conditioning, may certainly help.[47] However, these techniques deserve confirmation by prospective studies.

Another way is preoperative prehabilitation programs such as those used for fast-track procedures, including, among others, exercise rehabilitation.[48]

Moreover, light physical exercise may induce an inflammatory preconditioning that protects against exacerbated inflammatory stress consecutive to surgery.[49]

These 2 approaches implicate that the preoperative visit by the anesthetist occurs several weeks before surgery and that specialized facilities are available.

In the operating theater, prevention of CPSP is based on protective surgery and protective anesthesia/analgesia.

PROTECTIVE SURGERY

Acute postoperative pain and CPSP are linked to the surgical procedure. Therefore, it is judicious to speculate that surgery preserving nerve roots and producing minimal inflammatory reactions reduces the intensity of severe acute pain and the incidence of CPSP. This speculation was confirmed for groin hernia repair when techniques preserving nerves or materials inducing reduced inflammatory reaction were used.[50] No significant differences were, however, noted when open surgery was compared with laparoscopic approach.[51] Nevertheless, minimally invasive procedures should be recommended when applicable.

PROTECTIVE ANESTHESIA AND ANALGESIA

A critical question is whether anesthetic techniques can significantly influence the development of CPSP. Divergent opinions are found in the literature. Some investigators are convinced that surgery is the major determinant[50] and, consequently, that anesthetic techniques have little influence. Nevertheless, even if there exists no large prospective trial demonstrating that any specific anesthetic intervention reduces the risk of CPSP, anesthetic interventions can strongly influence the intensity of acute postoperative pain. Remember that acute postoperative pain intensity is an important determinant of the development of CPSP. In a cohort of patients recovering from general anesthesia, Aubrun and colleagues[52] reported that an important predictive factor of the severity of postoperative pain in the postanesthesia care unit is the dose of intraoperative opioids administered. Administration of intraoperative opioids promotes opiate-induced hyperalgesia with the consequence of increased postoperative pain.[53] To avoid this iatrogenic increase in the intensity of postoperative pain, anesthetists have to adopt opioid-sparing or opioid-protective anesthesia techniques. Opioids were introduced in the anesthetic paradigm in the mid-1960s mainly for their hemodynamic stabilizing effects and secondarily (incidentally) for their anesthetic-sparing properties.[54] At present, numerous alternatives are available for opioid sparing, that is, considering either nonanesthetic hemodynamic stabilizing drugs (ie, β-blockers) or anesthetic-sparing drugs, such as α_2-adrenergic agonists and combined locoregional/general anesthetic techniques. Moreover, ketamine, the dissociative anesthetic administered at antihyperalgesic dose, specifically protects against the hyperalgesic effects of opioids (see later).[55]

When considering specifically pain chronicization, the authors and other investigators have demonstrated, in a limited series of patients, that potent analgesia achieved with locoregional techniques combined with antihyperalgesic medications influences positively secondary surgery-related hyperalgesia and significantly reduces the incidence of CPSP after open colic surgery or thoracotomy.[12,18–56]

Before the anesthetic/analgesic strategies suspected to improve the incidence of CPSP can be detailed, 2 important remarks concerning the design of pain studies in the perioperative period are mandatory. In most cases, the choice of the studied population is based on a particular group of interventions or the type of surgery (gynecological, orthopedic procedures, or colectomy) and not on a particular risk. But for postoperative pain, some patients are more prone to suffer intense pain than others. Nevertheless, in many pain studies, the population recruited in the study was a mix of patients with different risk factors. This mixed recruitment introduces a serious flaw in the design of the study and thus the results.

In all the studies evaluating a drug or a technique to improve postoperative pain treatment, a precise evaluation of the specific pain risk of the patients (ie, using the Kalkman scale) should be presented to get an objective idea of the efficacy in the most-concerned population. The fact that this pain risk is not considered in the design of the studies may certainly account for the discrepancies found in the literature concerning the efficacy of various drugs and techniques. On the other hand, much attention is prompted on secondary hyperalgesia as an important determinant of CPSP. At present, how many studies on postoperative pain management consider parameters specific to secondary hyperalgesia?

Most studies in patients use the pain visual analog scale scores and/or a reduction in rescue (morphine patient-controlled analgesia) analgesic requirements as end points. These parameters do not measure secondary hyperalgesia or do so indirectly. The specific signs of secondary hyperalgesia, that is, the measurements of the area of hyperalgesia,[57] are quasi-never considered except in rare series. Moreover, prospective studies including an evaluation of a drug on the development of CPSP are particularly sparse when considering the mass of the data available on postoperative pain management. It is therefore not accurate to exclude any influence of analgesic techniques on CPSP because it is simply not known.

What is Protective Anesthesia/Analgesia

The aim of protective analgesia is to maximally reduce the importance of primary and secondary hyperalgesias, that is, to maximally reduce the excitatory input coming from the damaged periphery to the central nervous system and to put the central nervous system in a limited reactive state. For this purpose, it is advocated to use potent analgesic techniques combined with antihyperalgesics or drugs acting specifically on secondary hyperalgesia aimed at preventing the sensitization of the central nervous system, hence, to reduce the development of pathologic residual pain after surgery.[58,59]

What does potent analgesic techniques mean

In the context of prevention of intense acute postoperative pain and CPSP, it is clear that multimodal analgesia is mandatory. In this regard, the locoregional techniques are particularly interesting. These techniques provide a robust blockade of conduction for the influx of impulses arising from the injured area.[60] This blockade is, however, not sufficient to exclude any risk of CPSP. A meta-analysis including 458 patients (6 studies) failed to demonstrate significant difference in the incidence of chronic pain at 6 months with or without epidural technique.[61] This failure can easily be

explained by the fact that locoregional techniques have little influence on the excitatory inputs mediated by the proinflammatory factors released at the site of injury.

In the absence of contraindications, nonsteroidal antiinflammatory drugs (NSAIDS) have to be considered as part of a multimodal analgesic approach.[62] Products of arachidonic metabolism promote pain and hyperalgesia associated with tissue trauma and inflammation. Inflammation causes a widespread induction of cyclooxygenase (COX) 2 in the spinal cord neurons and other regions of the central nervous system elevating prostaglandin E_2 (PGE_2) levels in the cerebrospinal fluid. PGE_2 is a key mediator of both peripheral and central pain sensitizations.[63] NSAIDS, by COX inhibition, help to alleviate acute pain and probably influence the development of CPSP. In a retrospective study considering postthoracotomy neuralgia, Richardson and colleagues[64] reported an incidence of chronic postthoracotomy pain of 23.4% in patients treated for early postoperative pain with opioids alone versus 14.8% in patients benefiting from paravertebral blocks. The incidence decreased to 9.9% when NSAIDS were added. Of interest are the perspectives offered by the new class of analgesic substances acting on the peripheral nociceptors *TRPV1* (transient receptor potential vanilloid type 1).[65] These receptors are ionic channels located preferentially on sensory nerves that are activated by chemical ligands, such as capsaicin or resiniferatoxin; protons; and heat. These receptors participate in the nociceptive perception consecutive to chemical, thermal, and mechanical stimuli and are also responsible for the neurogenic inflammation by releasing proinflammatory mediators (calcitonin gene-related peptide, cholecystokinin, substance P) from the nerve. Substances acting on these receptors are awaited not only to block the nociceptives inputs immediately at the site of its generation but also to interfere very early with the trauma-induced proinflammatory reactions.[66,67] Clinical studies with highly purified forms of capsaicin instilled in the surgical wound at the end of procedure (groin hernia repair, total knee prosthesis) confirmed the lack of toxicity but reported only a modest positive effect on early postoperative pain.[68,69]

Opioids remain the cornerstone of postoperative analgesia. These drugs are particularly efficient to alleviate primary hyperalgesia (spontaneous pain).[70,71] As already mentioned, opioids induce short-lasting analgesia and long-lasting hyperalgesia. This opiate-induced hyperalgesia is also under the dependence of the excitatory neurotransmission.[12,55] Therefore, to prevent this condition, it is logical to associate an opioid with an antagonist of the excitatory neurotransmission (NMDA receptor), such as ketamine.[72] Moreover, there is evidence to suggest that morphine is associated with a better recovery profile than other synthetic opioids, such as fentanyl. Morphine, in contrast to the synthetic one, binds to the $\mu 3$ receptor (alkaloid specific) that is involved in the regulation of the inflammatory reaction[73] and may account for the positive effects on early postoperative rehabilitation observed in patients undergoing coronary artery bypass graft under morphine compared with fentanyl analgesia.[74]

ANTIHYPERALGESICS, DRUGS ACTING ON SECONDARY HYPERALGESIA

Several drugs are particularly effective in preventing secondary hyperalgesia (**Box 4**). These drugs are reported experimentally and/or clinically to reduce evoked (mobilization) pain, area of hyperalgesia surrounding the wound, and, for some, the incidence of CPSP. Most drugs are not potent analgesics for primary hyperalgesia or spontaneous pain or are even devoid of any analgesic effect. The authors focus on the most representative of these drugs.

Ketamine is the prototype drug to be used as the antihyperalgesic in the perioperative period. This drug is active against opioid- and trauma-induced hyperalgesias.

Box 4
Drugs or substances showing antihyperalgesic effects

- Ketamine/memantine/magnesium
- Gabapentin-pregabalin
- COX-1/2 inhibitors
- α_2-adrenoceotor agonists (perimedullary)
- Free radical scavengers (mannitol, vitamin C, and so forth)
- N_2O, systemic local anesthetics
- Drugs active against glial activity (minoxidil, propentofylline)
- Diet enriched with omega-3 or others

Ketamine reduces the incidence of postoperative residual pain.[6,56,57,75] It is a competitive inhibitor at the NMDA site of the excitatory glutaminergic transmission. Excitatory neurotransmission is involved in the propagation and amplification of nociceptive inputs at central site.[76,77] Ketamine is also documented to be an antiproinflammatory substance and helps to restore inflammatory homeostasis in the case of trauma and sepsis. Ketamine specifically reduces the production of proinflammatory cytokines by interaction with their nuclear transcription precursor the nuclear factor κB by a specific action on the purinergic receptors (adenosine 2A) and/or a reinforcement of the anti-inflammatory cholinergic reflex.[78–80] This property is original and not directly related to its antagonism at the NMDA receptor. This occurrence may explain why better results are obtained with ketamine than with other NMDA antagonists, such as magnesium.[81] The dose of ketamine required for the antihyperalgesic effect are significantly smaller (0.1–0.5 mg/kg $\pm$ 1–2 μg/kg/min during 48–72 hours) compared with the doses used for anesthesia.[72] Moreover, the antiproinflammatory effect of ketamine after one dose is particularly prolonged.

Ketamine is considered as an important element of the protective analgesic techniques, although this characteristic is not obvious in the meta-analysis evaluating the role of ketamine in postoperative analgesia[82,83] possibly because these meta-analyses are based on studies considering only the efficacy of this drug on primary hyperalgesia.

Gabapentin and pregabalin are 2 promising drugs under evaluation as antihyperalgesics in the perioperative period. Gabapentin and pregabalin are alkylated γ-aminobutyric acid analogues that were first developed clinically as anticonvulsants. These drugs are active in the treatment of chronic neuropathic pain. They bind to the $\alpha2/\delta$ subunits of voltage-gated calcium channels, thus preventing the release of nociceptive transmitters, including glutamate substance P and noradrenalin.[84] Despite some discordant results, several works report reduced incidence of chronic pain after surgery with the use of these drugs.[85–87]

These discrepancies are probably the result of a selection not taking into account population with comparable risk to develop CPSP.

The α_2-adrenoceptor agonists are interesting drugs to consider for multimodal analgesia and antihyperalgesia. Given by systemic route, these drugs potentiate the analgesic effects of the opioids (by a factor 4) without increasing their hyperalgesic properties.[88] Given by the spinal route, these drugs significantly reduce the area of secondary hyperalgesia when compared with bupivacaine or placebo and lower the incidence of CPSP after colonic surgery.[19] These effects are explained by the mechanism of action of the α_2-adrenoceptor agonists. These drugs mimic the effect of the

central descending inhibitory controls on pain perception, silencing the interneurons involved in the windup phenomenon.[89]

Recently, promising results are reported from drugs acting as glial modulator, such as propentofylline, a methylxanthine derivative. Raghavendra and colleagues[90] have shown that chronic propentofylline treatment in neuropathic rats attenuated the development of hyperalgesia and restored the analgesic efficacy of morphine. Propentofylline inhibits glial activation and enhances spinal proinflammatory cytokines after peripheral nerve injury. Moreover, in animals, modulation of glial and neuroimmune activations may restore the analgesic efficacy of morphine in the treatment of neuropathic pain.[91]

SUMMARY

Postinjury hyperalgesia is a physiologic phenomenon. In the perioperative period, for unknown reasons (at-risk populations, exacerbated proinflammatory process, anesthetics- and/or analgesics-induced pathologic hyperalgesia), this phenomenon can be deregulated, leading to CPSP. Large prospective epidemiologic studies are mandatory to determine the exact incidence, favoring factors, and effect of the different anesthetic techniques of this phenomenon.

Prevention of CPSP is of critical concern for the anesthetist because, once established, it is as invalidating and difficult to treat as many other chronic pain conditions.

For this purpose, it is important to identify preoperatively patients who are prone to develop CPSP. Preoperative mental and physical preparations for the surgical stress should be initiated when possible. Protective surgical and anesthetic techniques, that is, techniques that avoid trauma to nerves, with reduced inflammatory stimuli, should be chosen. It is important to avoid the potential for opioid-induced hyperalgesia with the use of analgesic treatment combining potent analgesics and efficacy-proven antihyperalgesics.

For anesthetists it is important to follow-up the effect of such strategies on the occurrence of CPSP for both short and long terms. This follow-up helps to identify the onset of CPSP early and initiate the early treatment of patients with CPSP and to validate the efficacy of the preventive strategies.

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