Chronic post-surgical pain

Cerrahi sonrası kronik ağrı

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Summary

Chronic postsurgical pain (CPSP) has lately become a neglected phenomenon. However, in recent years, investigations of the possible risk factors (type of surgery, preoperative pain, acute postoperative pain, and psychological and genetic factors) have also gained as much importance as the clinical problem. CPSP is not only observed following major surgery, but also following minor surgical procedures, such as hernia and vasectomy. Definitive data regarding the incidence of CPSP have not been obtained yet, since it is difficult to develop standard methods to resolve this difficult and complicated clinical picture. Many different medications, such as gabapentin, ketamine, venlafaxine, lidocaine, tramadol, and steroids have been tested in addition to multimodal analgesic techniques for the management of CPSP. Hence, preventive analgesia is a broader application of preemptive analgesia that includes any preoperative analgesic regimen able to control the sensitivity induced by pain.

Key words: Chronic pain; postoperative analgesia; preventive analgesia.

Özet

Cerrahi sonrası kronik ağrı (CSKA) son zamanlara dek görmezden gelinen bir fenomendi. Ancak son yıllarda sorunun klinik önemi kadar olası risk faktörleri de (type of surgery, preoperative pain, acute postoperative pain, psychologic and genetic factors) önemle incelenmeye başlanmıştır. CSKA sadece majör cerrahi girişimlerden sonra değil aynı zamanda herni ve vazektomi gibi minör cerrahi girişimlerden sonra da görülebilmektedir. CSKA insidansı ile ilgili kesin verilere henüz ulaşılamamıştır. Çünkü bu zor ve karmaşık klinik tablonun çözümünde standart yöntemler geliştirmek güçtür. CSKA tedavisinde multimodal analjezik teknikler kadar birçok farklı ilaç da (gabapentin, ketamine, venlafaksin, lidokain, tramadol, steroidler v.d.) denenmektedir. Bu nedenle, koruyucu analjezi ağrıyla uyarılan duyarlılaşmayı kontrol edebilen herhangi bir ameliyat öncesi analjezik rejimi içeren premptif analjezinin daha geniş bir uygulamasıdır.

Anahtar sözcükler: Kronik ağrı; postoperatif analjezi; koruyucu analjezi.

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Introduction

Chronic postsurgical pain (CPSP) is a clinical picture persisting for at least three months following a surgical intervention, where additional particular neuropathic symptoms are observed. The problem may also be defined as a long-term "*acute neuropathic pain*". Pain developing consequent to malignancy and chronic infection should not be included in this picture. Besides, some clinical pictures with pain in the preoperative period may not be included in CPSP classification (e.g. post-laminectomy syndrome). The first paper on chronic post-surgical pain (CPSP) was published by Crombie and colleagues ten years ago.[1] Later, many prominent reviews were published on this subject.[2,3] Although CPSP was accepted by surgical disciplines as negligible and "*normal*" up until recent times, it has now come to be an important clinical, or even social, problem. CPSP may occur following major surgery (amputation, hip replacement), as well as following minor procedures (herniorraphy, vasectomy).

While describing CPSP in this review, we will also mention about the clinical importance, mechanisms, risk factors, prevention, and treatment options of this pain.

Clinical Importance of the Problem

There are many factors affecting the incidence of CPSP. There are variances in the incidence of CPSP with regard to different operative procedures and different studies. However, its commonness is undisputed. The approximate incidences of chronic pain after certain procedures have been displayed in Table 1.

Although it is possible to find statistical data on operations performed in our country through the web site of the Ministry of Health, access to the results of CPSP is impossible. Nevertheless, access to some statistics from USA and England is possible. Reports and postoperative chronic pain incidences of the following eight major operations in 1994 in USA, and in 2005 and 2006 in England have been published: mastectomy, cesarean section, amputation, cardiac surgery, hernia repair, cholecystectomy, hip prothesis surgery, and thoracotomy.[4,5]

The incidence of postoperative chronic pain in corresponding years was calculated as 1.8-6.7% in USA, and 0.5-14% in England. After all, even these results, which are questionable for reliability (differences in surgical technique, study design, patient population, descriptions and so on) give us an idea regarding the size and importance of the problem. Being an important public health issue affecting a significant number of patients, CPSP has serious economic consequences, as well as significantly affecting the quality of life.[6,7]

Although it is impossible to explain the causes of

Table 1. Estimated incidence of chronic postoperative pain after some surgical procedures

Type of operation	Incidence of chronic pain (%)
Mastectomy	20-50
Thoracotomy	30-50
Hernia repair	5-35
Amputation	50-85
Caesarean section	6-10
Hysterectomy	32
Hip arthroplasty	28
Coronary artery bypass surgery	30-50
Vasectomy	5-18
Cholecystectomy	26
Colectomy	28

CPSP in detail, some strategies may be developed to decrease its incidence. There are many factors determining the development and incidence of CPSP. The type of surgical operation is the leading factor. For example, development of CPSP reaches up to 85% following operations such as amputation, whereas this rate is less than 1% following cataract surgery,[8] Another factor is the different approach techniques in surgical interventions.

There are certain differences between the anterior approach and classical posterolateral approach in thoracotomy procedures regarding the development of CPSP. In the former surgical approach, the incidence of CPSP was observed to be about 31%, while in the latter, this ratio was reported to be approximately 50%.[9,10] Psychosocial causes are the leading risk factors for development of CPSP, as well as surgical causes.

Mechanisms

CPSP develops through complex unclear mechanisms. Various mechanisms are responsible for the different pain syndromes, even following the same operation. For instance, phantom pain, stump pain and back pain following lower limb amputations.[11]

CPSP occurs either as a consequence of a present inflammation, or more commonly, as a manifestation of neuropathic pain caused by surgical injury to major peripheral nerves. Inflammatory pain occurs as a result of an increased sensitivity of pain, appearing in response to tissue injury and inflammation. It develops as the result of the release of sensitizing inflammatory mediators, which lead to a decrease in the threshold of nociceptors innervating the inflammated tissue (peripheral sensitization). Consequent to an increase in the excitability of neurons in the central nervous system (central sensitization), inflammatory pain comes to be associated with exaggerated responses to regular sensory inputs. Neuropathic pain is pain developing following injury to nerves and the sensory transmission systems in the spinal cord and the brain.

In the immediate postoperative period, the clinical picture is dominated by spontaneous resting and breakthrough pain referring to the surgical site and its vicinity, which develops through direct activation of nociceptors, inflammation, and in some cases, by injury to nerves.[12]
In the event of injury to nerves during surgery, a neuropathic component of pain may immediately develop and persist in the absence of any peripheral noxious stimuli or ongoing peripheral inflammation.

The sequence of pain must be kept in mind when explaining the mechanisms of CPSP: surgical nerve injury →neuronal plasticity → pain.

Surgical Nerve Injury

In clinical practice, CPSP is observed as neuropathic pain in many patients.[13] Injury to major nerves passing through the operation site is the prerequisite for development of CPSP. In a small group of patients, a continuous inflammatory response can contribute to maintained inflammatory pain, such as that following inguinal mesh hernia repair.[14] According to late period electromyography findings, following thoracotomy, injury of up to 50-100% to the intercostal nerve conduction around the incision is observed.[15] Moreover, the degree of nerve damage, which is evaluated by changes in the sensory threshold and somatosensory evoked responses to electrical stimulation in the thoracotomy scar area, correlates with the intensity of chronic pain.[16]

However, there are clinical studies that contradict these investigations. Maguire et al. applied electrophysiological tests onto thoracotomy patients preoperatively, immediately after the operation, and on the postoperative sixth week and third month, and they could found no relation between intercostal nerve injury and chronic pain.[17] At what level should the lesion(s) be in order to cause neuropathic pain by nerve injury? And which injury-prone tissues other than nerves must be kept in mind in development of neuropathic pain? Finally, it is necessary to investigate the contributions of central and peripheral changes in the nervous system to this picture.

Neuronal Plasticity and Pain

1- Peripheral nerve injuries lead to neuroimmune interactions. When an axon is severed, the distal end

undergoes degeneration and engulfment by inflammatory cells. Pain-inducing signal molecules such as tumor necrosis factor (TNF) are secreted, which increase the ectopic activity in axons.[18] Microglia, which are central macrophage-like cells, are activated to a great extent in the spinal cord, producing signal molecules that act on the dorsal horn neurons, which in turn produce pain hypersensitivity.[19]

2- The dorsal horn is the site at which altered activity and gene expression occur, producing central sensitization, loss of inhibitory interneurons and microglial activation, resulting in amplification of sensory flow.

3- The descending controls in the brainstem modulate the transmission in the spinal cord. The limibic system and the hypothalamus play roles in altered mood, behavior and autonomic reflexes.

4- Sensation of pain is generated in the cortex (past experiences, cultural inputs and coverage of expectations determine the sensations felt by a patient).

5- The genomic DNA in patients may or not predispose to chronic pain and affect the reaction to treatment.[12]

It has been shown in animal and human studies that peripheral nerve trauma may induce neuroplastic changes in the central nervous system (central sensitization) causing abnormal sensory input discharge through the injury site following wound healing.[20,21]

Risk Factors

Identification of risk factors for CPSP is important, because it provides a possibility for preventing such pain. Risk factors may be classified as patient-related and medical factors. Each patient developing CPSP has a specific genotype, medical history, experiences, beliefs, and psychosocial conditions related to this problem. Some risk factors emphasized in the development of CPSP are as follows;

Demographic Factors

Advanced age has been reported as a risk factor in some operation types. Young women undergoing breast surgery have a larger mass and experience more discomfort in the acute postoperative period and develop CPSP more frequently.[22] Smith et al. compared the post-mastectomy CPSP in different age groups and found that the younger age group had a higher incidence of CPSP. Chronic pain was observed in 65% of the 30-49 age group, in 40% of the 50-69 age group, and in 26% of the over-70 age group.[23] Proobalan et al. reported similar rates for the incidence of chronic pain following hernia operations.[24] On the other hand, in some clinical studies, postoperative pain is more frequently observed in women than men.[25,26] The importance of other demographic factors such as employment, housing and marital status, remains controversial.

Genetic

In the general population, sensitivity to physiological nociceptive and clinical pain may vary in different individuals. This variation with regard to the generation and pain experience may also reflect different responses.[27,28]

Correlation with elevated catecholamine-O-methyltransferase (COMT) has been shown to be a risk factor in chronic temporomandibular arthralgia. Diatchenko et al. also showed a correlation between genetic polymorphism and temporo-mandibular joint disorders.[28] Devor M. hypothesized that certain people are predisposed to development of pain after nerve injury.[29] Studies in rodents have revealed results suggesting the susceptibility to develop pain to have a strong heritable component, but that the genes responsible for this inheritance remain to be identified.[30,31] Many investigators have suggested that some clinical disorders (fibromyalgia syndrome, migraine, irritable bowel syndrome, irritable bladder, Raynaud's Syndrome) may be markers of post-injury chronic pain.[32,33]

Acute Postoperative Pain

Many studies on development of CPSP have been published about the importance of sufficient treatment of postoperative pain in the acute period. Among these, hernia surgery, breast cancer surgery and total hip arthroplasty operations may be stated.[14,34,35]

The most important dilemmas are probably related to the medications and methods used. In previous

studies, ketamine was reported to have a limited acute postoperative analgesic efficacy, with long term effectiveness in antihyperalgesia being to a higher extent.[36,37] It has been suggested that epidural anesthesia at first is effective in preventing central sensitization during surgery; however, different opinions on this subject were also put forth later.[38]

Preoperative Pain

It has been stated that the presence of preoperative pain in patients may be related to CPSP. Hernia operations may be leading among these operations. In a study on patients undergoing hernia operation, Page et al. found that about a quarter of the patients did not have pain at rest before their hernia repair, and that half had mild pain, with the remainder having mild to moderate pain at rest.[39]

As expected, a higher number of patients suffered pain on movement. While 25% of the patients did not complain from pain in the follow-ups in the first year, 22% complained of pain on movement. Some of the patients who had no pain preoperatively, developed pain after the repair operation and 5% of the patients stated that the quality of their daily life was lower a year after surgery.

In a study by Nikolajsen et al., they suggested that pre-amputation pain increased the risk of stump and phantom pain.[40] Keller and colleagues showed that 48% of those in whom narcotics had been given prior to thoracotomy, developed chronic post-thoracotomy pain, compared to a mere 5% of those who received no narcotics.[41] While a similar relation was stated between mastalgia and phantom breast pain, this correlation was not established in total hip arthroplasty operations.[35,42]

Surgical Factors

Some important surgical factors may be related with the development of CPSP. Duration of the operation, surgical technique (laparoscopy vs. open), incision site and type, experience of the surgeon, and the center where the intervention is performed are included in these factors. Peters et al. found more chronic pain and poorer outcomes in general, in operations lasting for more than 3 h.[43]

This is not surprising as these patients probably have more serious pathologies, complications or other health issues affecting both the complexity of the operation and the outcome. A relation affecting the incidence between different operation techniques and chronic pain following breast surgery has been put forth.[44]

The incidence varied from 53% for mastectomy with reconstruction by implant, to 31% for mastectomy only, to 22% for breast reduction. However, a relation between different open techniques and CPSP following hernia operations can not be found, while less pain was observed by laparoscopic procedures.[45] In the same way, it has been reported that CPSP is seen more frequently in open cholecystectomy than laparoscopic technique.[46]

It has been suggested that chronic pain following hysterectomy is partially lower in procedures performed through a Pfannenstiel incision.[47] Similarly, protection of the nerve in the operation site or the neighborhood in the preoperative period may decrease the incidence of CPSP development. For example, preservation of intercostal brachial nerve in mastectomy operations and the intercostal nerve in thoracotomy may decrease the incidence of postoperative chronic pain. It is a fact that the experience of the surgical team affects the morbidity and mortality.

Tasmuth et al. stated that CPSP following breast surgery was observed more common in surgical units with a lower number of cases and limited experience.[48] On the other hand, it has been stated in some studies that radiotherapy or chemotherapy may increase the risk of chronic pain. Radiotherapy following breast cancer operations has been reported to increase the risk of chronic pain.[34]

Is there a relation between CPSP, anesthetic medications and methods? There is no definite answer to this important question yet. In the latest published study of Fassoulaki et al., a positive relation was not found between anesthetic agents used (Sevoflurane, Desflurane, Propofol) and acute postoperative pain.[49] In another study on chronic pain one year after hysterectomy, Brandsborg et al. found chronic pain in 14.5% of spinal anesthesia-administered

cases and 33.6% in general anesthesia-administered cases.[47] In the same study, observation of a lower frequency of chronic pain in spinal anesthesia cases and not epidural anesthesia, was explained by the stronger blockade of "*central impulse traffic*" in spinal anesthesia. Similarly, in cesarean section operations compared for spinal and general anesthesia, the incidence of chronic pain was higher in the latter group at the end of one year.[50]

Psychosocial Factors

There are many articles related with the effects of psychosocial factors on acute postoperative pain. Katz et al. concluded that preoperative anxiety is a risk factor in the development of pain for up to 30 days following breast surgery.[26] The incidence of acute postoperative pain is affected by catastrophization (exaggerated negative beliefs and response).

There have only a few studies on the influence of psychosocial factors on chronic pain following surgery, the results of which are contradictory. Katz et al. studied depression and anxiety in patients with or without pain following thoracotomy and concluded that preoperative assessment may affect the results.[51] In another study on women undergoing breast cancer surgery, those with increased preoperative anxiety and depression had a lower degree of anxiety but still had a higher degree of pain and depression in the postoperative first year.[52]

Peters et al. performed a study on the somatic and psychosocial predictors of long-term unfavorable outcomes after surgery.[43]

The most significant predictors were found to be duration of the operation (longer than three h) and severe postoperative pain. Fear of surgery was associated with more pain, poor recovery and a poor quality of life six months postoperatively. According to the study, despite the fact that optimism resulted in better recovery and a better quality of life, chronic pain and physical functions were not affected. In a study on 70 lower limb amputees, psychosocial variables such as catastrophization, perceived social support and solicitous responding one month after the amputation, predicted phantom pain for up to to years following the amputation.[53]

Newer and further studies are necessary to study the interaction between CPSP and psychosocial factors. Instruments used in measuring the variables may need to undergo modification in order to suit the specific conditions. Further prospective studies, including preoperative quantitative sensory testing, may reveal the precise contribution of preoperative sensitization to postsurgical pain.

Prevention

Since treatment of CPSP is difficult due to various reasons, its prevention is an easier task. However, it is not easy to develop efficient strategies in clinical practice. Elimination of risk factors such as not undergoing the surgical procedure and failure in effective pain control may compose the principle of these strategies. The principle risk factor for developing CPSP is the surgical procedure itself; hence, avoiding the procedure is the method of prevention. Since this may not be possible, surgical indications can probably be assessed meticulously or conditions leading to surgery may be hindered. One way of preventing phantom pain secondary to amputation may be to control smoking and diabetes.

Better determination of surgical necessity will be effective in preventing CPSP. In a study evaluating pre- and post-operative pain in inguinal hernia surgery, patients without preoperative pain were observed to suffer from significant pain perception following surgery. The pain before surgery resolves following surgical interventions.[39] Vigilant waiting has been shown to be safe in patients with asymptomatic inguinal hernias.[54] Previous studies have indicated that in general, emotional distress and anxiety are associated with greater acute pain.[51] Therefore, particularly in oncologic surgery, consideration of emotional conditions of CPSP patients and stress relieving methods may be effective in preventing CPSP.

Nowadays, various medications and techniques are used with regard to effective postoperative pain control in practice. Preemptive analgesia is defined as anti-nociceptive treatment which prevents the establishment of altered central processing of an afferent input that amplifies postoperative pain.[55] It is thought that by decreasing the altered central sensory processing, preemptive analgesia consequently

decreases the incidence of hyperalgesia and allodinia following surgery.[56]

In a meta-analysis on 3261 patients and 66 studies investigating the efficacy of prophylactic analgesia on acute postoperative pain treatment, the efficacy of epidural analgesia, local anesthetic wound infiltration, systemic N-methyl-d-aspartate (NMDA) receptor antagonists, systemic non-steroidal anti-inflammatory drugs (NSAIDs) and systemic opioids in various operations with respect to pain scores, analgesic consumption, time to rescue analgesics, have been investigated.[57]

The result of these outcome measures revealed that preemptive analgesia showed an overall beneficial effect in selected analgesic regimens that were the most pronounced following epidural analgesia, local wound infiltrations and systemic NSAID administration. Recently, the concept of preemptive analgesia has begun to gain importance to expand into preventive analgesia.[58]

Despite the fact that timing of preventive analgesia is not mandatory, pre-incisional analgesia may block the stress response during surgery. Adequate preventive analgesia should include multimodal techniques with several drugs to decrease peripheral and central hypersensitivity.[59] In four studies in which magnesium was used, Mc Cartney et al. reported that systemic application of NMDA receptor antagonists ketamine or dextrometorphan resulted in preventive analgesic effects, but that no positive effects were observed.[60]

Lavand'homme et al. demonstrated the combination of epidural analgesia with systemic application of ketamine to decrease the area of hyperalgesia surrounding a surgical incision in patients following colectomy, and to affect the late residual pain. [61] Hence, there is concrete evidence that systemic NMDA- receptor antagonists are able to induce a preventive effect in the perioperative period and that they may enhance the efficacy of treatment of acute and prolonged post-surgical pain. In spite of the discordance between recent clinical studies, not only the timing of analgesia management, but duration and efficacy of analgesic interventions are also important to treat pain and postsurgical hyperalgesia.[62,63]

Gabapentin, an anticonvulsant that can produce analgesia by binding to and inhibiting the pre-synaptic voltage-dependent Ca2+ channels, decreases the influx of calcium and hence, inhibits the release of neurotransmitters including glutamate from the primary afferent nerve fibers that synapse on and activate pain-responsive neurons in the spinal cord.[64]

In a meta-analysis evaluating the effects of preoperative gabapentin on postoperative pain in 12 randomized controlled studies and 896 patients, it was shown that oral gabapentin administered within four hours before surgery has a significant postoperative analgesic effect.[65] Furthermore, in this meta-analysis, in clinical studies evaluating gabapentin for chronic neuropathic pain, the target doses ranged from 600 mg/d to over 3600 mg/d in divided doses with the treatment periods ranging from one week to several months. Preoperative oral gabapentin appears to be a useful adjunct for the management of postoperative pain. Gabapentin may provide synergistic analgesic effects when combined with other agents.[66,67] Since gabapentin has been demonstrated to attenuate sensitization in a variety of settings, preoperative use of oral gabapentin may contribute to a decrease in the incidence and severity of chronic postsurgical pain.[68,69]

There are several ways to find new targets for these purposes. Opioid receptors have recently been identified on the peripheral processes of sensory neurons. These findings have provided new insight into intrinsic mechanisms of pain control, and suggest innovative strategies for developing drugs and different approaches to treatment of pain.

Several drugs and drug classes have been shown in animals to reduce hyperphenomena following tissue injury: glutamate receptor antagonists, alfa 2 adrenergics (clonidine), serotonin inhibitors (amitriptyline, ketanserine), glucocorticosteroids, cyclooxygenase inhibitors and specific sodium channel blockers.[70,71]

Canabinoid receptor 2 (CB2) agonists are used in

the treatment of chronic pain states without CNS (Central Nervous System) effects associated with CB1 receptor activation. Studies on animal models suggest that they act mainly via non-neuronal cells, possibly be inhibition of inflammatory cells in the periphery or the CNS, or via release of beta-endorphin. However, the clinical relevance and mechanism of analgesic action remain uncertain.[72]

Conclusions

CPSP following surgery is a common entity. However, there is still no standardization in the strategies for prevention and treatment of this complicated clinical problem with respect to technique and organization. Therefore, it would be appropriate to evaluate patients who will undergo surgery, beginning from the surgical decision, and to determine the anesthesia and postoperative pain management initially. The concept of postoperative analgesia should involve both the preoperative and postoperative periods.

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