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Vol. XIX, Issue 1 January 2011

Chronic Pain after Surgery or Injury

The first publication that identified injury and surgery as major risk factors for chronic pain appeared in 1998.[1] This paper reported that around 40% of 5130 chronic pain patients in 10 pain clinics in the United Kingdom had developed their chronic pain problem after surgery or trauma. This finding has led to a dramatic increase in interest in this subject; searches on PubMed for key words such as chronic or persistent post-surgical pain now reveal hundreds of publications on this topic. While most of these papers analyze pain after surgery,[2,3] the original publication also suggested trauma as another major precursor of chronic pain.[1] This suggestion has been confirmed by subsequent studies[4]; in principle, every chronic pain has been acute pain at some stage.[5] The problem is not limited to major surgery or major trauma, as even minor operations such as herniotomy can have significant consequences with regard to development of chronic pain; a recent editorial on this topic states that "chronic pain is the most common and serious long-term problem after repair of an inguinal hernia."[6] The consequences of chronic postsurgical or post-traumatic pain are significant, not only in terms of suffering and reduced quality of life for the individual patient but also with regard to the subsequent costs to the health care and social support systems of our societies.[4,7]

Furthermore, persistent postsurgical pain is an area that might enable us to better understand the development of chronic pain in general, as it provides an ideal setting for the study of risk and protective factors in a very controlled environment.[5]

Definition and Epidemiology

A publication by the International Association for the Study of Pain (IASP) defines persistent postsurgical pain as pain that develops after surgical intervention and lasts at least 2 months[8]; other causes for the pain have to be excluded, in particular pain from a condition preceding the surgery. This definition has been criticized as overly simplistic. In particular, the time frame of 2 months has been questioned, because we have insufficient data to know if pain is still subsiding 2 months after surgery, possibly due to ongoing inflammatory processes lasting more than 2 months after some operations.[9] This suggestion is in line with studies that show a continuous decline in the incidence of chronic pain over the first 6 months after surgery. Depending on the definitions applied, data on incidence vary significantly (see Table 1). Overall, the incidence of chronic pain after major surgery is estimated to lie in the range between 20% and 50%; relatively minor operations such as inguinal hernia repair or a C-section seem to lead to this problem in around 10% of patients.[3] Overall, the estimated incidence of severe disabling pain after surgery is in the range of 2–10%.[2]

Supported by a grant from Endo Pharmaceuticals, Inc., USA

Table 1 Incidence of chronic pain after surgery		
Type of Operation	Incidence of Chronic Pain (%)	Estimated Incidence of Chronic Severe Pain (>5 out of 10) (%)
Amputation	30–85	5–10
Thoracotomy	5–65	10
Mastectomy	11–57	5–10
Inguinal hernia	5–63	2–4
Coronary bypass	30–50	5–10
Cesarian section	6–55	4
Cholecystectomy	3–50	Not estimated
Vasectomy	0–37	Not estimated
Dental surgery	5–13	Not estimated
Source: Reproduced with permission from: Macintyre et al.[33]		

Pathophysiology

There is ongoing discussion about the nature of persistent postsurgical pain. While it was initially thought that persistent postsurgical pain is primarily a neuropathic pain, there is now increasing discussion that in some patients, ongoing nociception might be playing a role in this condition.[2] The initial notion that persistent postsurgical pain is usually of a neuropathic nature was promoted by the observation that operations with major nerve damage such as thoracotomy, mastectomy, or amputation are associated with the highest incidence of such pain.[2, 3] Furthermore, a study in postherniotomy pain syndrome showed that all patients with this type of pain had features of neuropathic pain.[10] This finding is also in line with other pain states with a neuropathic component, where acute pain progresses to chronic pain, such as acute back pain progressing to chronic back pain (often along with sciatica), and shingles leading to postherpetic neuralgia. However, a number of patients with persistent postsurgical pain do not show any features of neuropathic pain or any sensory changes such as hypoesthesia, making it difficult to fit one pathophysiological concept to all patients with chronic pain after surgery.[11] The ongoing debate on this issue suggests that future studies in this area need to involve neurophysiological assessment and clear classification of pain as neuropathic or nociceptive.[9]

Predictive Factors

Predictive factors for persistent postsurgical pain can be patient specific or surgery specific.[7] Furthermore, these factors can be subdivided into preoperative, intraoperative, and postoperative factors (Table 2). One relevant factor may be a genetic disposition to increased pain susceptibility. Over recent years, a number of single nucleotide polymorphisms (SNPs) have been identified. One of the best studied conditions is the functional genetic polymorphism of catechol-*O*-methyltransferase (COMT); specific haplotypes of this enzyme are not only involved in determining heightened sensitivity to experimental pain, but also seem to correlate with an increased risk of developing chronic temporomandibular joint pain.[12] Similarly, there seems to be a haplotype of the enzyme GTP-cyclohydrolase (GCH1) that reduces pain sensitivity to experimental stimuli and also was found to reduce the incidence and severity of pain in patients with cancer, as well as in patients who had undergone laminectomy 1 year previously to treat a prolapsed disk.[13] Despite this progress, none of these genetic factors have been identified as specific markers for the generation of chronic pain after surgery. Other preoperative risk factors are gender and age.[2, 3] Females, who show increased incidence of most chronic pain syndromes, also have an increased risk of developing persistent postsurgical pain.[7] Younger patients seem to carry an increased risk of developing persistent postsurgical pain, although this trend is not true for postherpetic neuralgia. A recent study also showed a reduced incidence of post-thoracotomy pain syndrome in children and adolescents.[14]

Preoperative pain is consistently found to be a predictor for persistent postsurgical pain, which might reflect an independent risk factor, but could well be a manifestation of predisposing factors.[2,3,7]

Hypervigilance, thought to be one of the psychosocial factors contributing to fibromyalgia, may also play a role in persistent postsurgical pain

With regard to psychosocial factors, a systematic review identified depression, psychological vulnerability, stress, and rate of return to work as predictors for persistent postsurgical pain.[15]

Table 2 Risk factors for chronic postsurgical pain
Preoperative Factors
Pain, moderate to severe, lasting more than 1 month Repeat surgery Psychological vulnerability (e.g., catastrophizing) Preoperative anxiety Female gender Younger age (adults) Workers' compensation Genetic predisposition Inefficient diffuse noxiou inhibitory cntrol DNC
Intraoperative Factors
Surgical approach with risk of nerve damage
Postoperative Factors
Pain (acute, moderate to severe) Radiation therapy to area Neurotoxic chemotherapy Depression Psychological vulnerability Neuroticism Anxiety
Source: Reproduced with permission from Macintyre et al.[33]

Hypervigilance, thought to be one of the psychosocial factors contributing to fibromyalgia, may also play a role in persistent postsurgical pain.[16] Another predictive construct might be catastrophizing, although the question of causality remains unanswered here.[5]

Recent research has concentrated on preoperative experimental predictors of persistent surgical pain because the results might permit stratification for risk. Such assessment of experimental predictors has concentrated on both static and dynamic assessments of neurophysiological function.[5] The results for simple sensory phenomena such as pain thresholds and pain tolerance thresholds have been disappointing with regard to their predictive role.[7] However, dynamic assessments of the quality of the endogenous inhibitory system by diffuse noxious inhibitory control (DNIC)[17] seem to be more promising. The same may be true for assessments of the excitatory system by measuring temporal summation.[7]

Relevant intraoperative risk factors might be the surgical approach and the anesthetic technique. With regard to the surgical approach, the duration of the operation as well as the surgical technique seem to be important; operations that reduce nerve injury, such as minimally invasive techniques, or operations aiming to preserve nerves seem to be superior here.[2,3,7] With regard

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to anesthesia, there are retrospective data for hysterectomy[18] and C-section[19] that show a protective effect of spinal anesthesia in comparison to general anesthesia, with a relative risk reduction in the range of 50%. In the case of both surgery and trauma, the need for reoperation or the development of bleeding or infection seems to increase the risk of persistent postsurgical pain.[7]

The most relevant postoperative factor seems to be the severity of acute postoperative pain.[2,3,7] Multiple studies have consistently found a strong correlation between the severity of acute postoperative pain and the development of persistent postsurgical pain.[17] These findings are consistent throughout the whole range of surgeries investigated. It is important to note that the overall (median) severity of pain over the first 7 days after surgery was a better predictor than the maximum pain score,[20] and thus the duration of severe postoperative pain may also be relevant.

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However, particularly with regard to this risk factor, it is very difficult to differentiate between causality and association. It may well be that patients with severe acute postoperative pain experience more sensitization and therefore develop more persistent postsurgical pain. However, it could also be that these patients have ongoing preoperative pain, and then severe postoperative pain would not be an independent risk factor. Last, but not least, these patients might have severe acute postoperative pain because the precursors of persistent postsurgical pain are already developing in the early postoperative period.

Preventive Approaches

As chronic pain is notoriously difficult to treat, it would be desirable to find methods to prevent the development of persistent postsurgical pain. The high incidence of persistent postsurgical pain needs to be considered in the indications for surgery. If we acknowledge, for example, that some patients with no pain before

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a herniotomy will have pain afterwards, then it might be appropriate not to operate on every asymptomatic inguinal hernia.[6] Similar caveats might be considered in patients with visceral hyperalgesic syndromes such as irritable bowel disease and interstitial cystitis, and they could apply to situations such as male sterilization or cosmetic surgery because persistent pain has been shown to be a problem after vasectomy[21] and cosmetic breast augmentation.[22]

Some preventive measures, such as changing the surgical approach, have already been touched on in the discussion on risk factors. Similarly, the use of regional anesthesia seems to be promising, and studies have confirmed the benefit of using regional analgesia techniques in the postoperative period. The results here are not completely consistent, but they do show benefits with the use of epidural analgesia after thoracotomy,[23] colectomy,[24] and amputation,[25] with the use of a peripheral nerve blockade such as paravertebral blockade after mastectomy,[26] or even with the use of local infiltration or topical administration of local anesthetics.[27] However, these results are currently rather arbitrary findings and do not permit the development of appropriate treatment protocols, in particular with regard to the type, intensity, and duration of regional techniques provided.

With regard to pharmacological measures, it is not surprising that the use of drugs that have effects on central sensitization has shown benefit in some settings. The two drug types that have been used are the NMDA-receptor antagonist ketamine[24] and, more recently, the alpha-2-delta ligands gabapentin and pregabalin.[28] Operations where these drugs have been used successfully include mastectomy, laminectomy, total knee joint replacement, hysterectomy, and colectomy. However, there are currently insufficient data for all three compounds to suggest the necessary protocol or the duration of treatment required. With regard to pregabalin, for example, most studies with a single premedication dose show no beneficial effect. However,

2 weeks of perioperative treatment reduced neuropathic pain 3 and 6 months after total knee joint replacement from an incidence of 9% and 5%, respectively, to zero.[28]

Last, but not least, it may well be that simple provision of good analgesia in the postoperative period has a preventive effect. In an impressive study, patients who had received hip or knee replacement received either standard-of-care analgesia or good background analgesia with access to breakthrough medication for breakthrough pain and preemptive administration of breakthrough medication 1 hour before physiotherapy.[29] When this treatment was given in the first few weeks after surgery, at any follow-up for the next 24 weeks, significantly fewer patients in the group receiving the superior analgesic regimen had moderate to severe pain on ambulation compared to patients in the control group.

Future Developments

The area of persistent postsurgical pain requires a major research initiative, as suggested in a series of editorials in *Anesthesiology* in March 2010.[9,30,31] First and foremost, we need to understand the mechanisms of persistent postsurgical pain better, and we therefore need to develop valid preclinical models.[31] Second, we need to design better clinical studies that take a prospective, procedure-specific approach to the identification of all risk factors and include long-term follow-up with ongoing assessment of neurophysiology, evidence-based diagnosis

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of pain, and careful description of all procedures.[9] Therapeutic interventions that aim at prevention must then be performed in studies that carefully collect such data. The outcome of such studies should be the evidence-based identification of patients at higher risk and the development of appropriate therapeutic interventions to prevent the development of persistent postsurgical pain. A careful study design adhering to these suggestions has recently been published.[32] It includes the determination of all relevant demographic, psychosocial, and pain-related factors as well as the assessment of mechanical temporal summation and diffuse noxious inhibitory control. The investigators plan to publish measurements of wound hyperalgesia, a study of genetic factors, and results of a 12-month follow-up.

It is important, in particular for more aggressive preventive strategies, that the population at risk should be identified to avoid unnecessary exposure of patients to high-risk preventive treatment.[30] Future options for treatment might include the use of growth factors such as nerve growth factor (NGF), blockade of "pain-specific" sodium or calcium channels, or treatments aimed at increasing the function of inhibitory systems.[2]

Practical Conclusions

Persistent postsurgical pain is a common but underdiagnosed and underrecognized complication of surgery that has significant consequences for the individual patient and for society as a whole. Information on persistent postsurgical pain needs to become a component of informed consent for surgery, and the risk needs to be considered in decisions on appropriate indications for surgery. However, patients also must be informed that the development of persistent postsurgical pain does not suggest a failed operation or a surgical mistake. Relevant risk factors for the development of persistent postsurgical pain are younger age, female gender,

Relevant risk factors for the development of persistent postsurgical pain are younger age, female gender, chronic pain states, psychosocial factors, and genetic predisposition

chronic pain states, psychosocial factors, and genetic predisposition. There are also intraoperative risk factors, in particular traumatic surgery with an increased risk of nerve injury. Severe acute postoperative pain is a major predictor for pain in the postoperative period. Preoperative neurophysiological assessments might identify patients at increased risk.

Approaches that might have a preventive effect include the use of surgical techniques that reduce nerve damage, the use of regional anesthesia and analgesia techniques, and the administration of antihyperalgesic compounds such as gabapentin, pregabalin, and ketamine. There are insufficient data to suggest ideal treatment protocols, and carefully designed preclinical and clinical research in this area is urgently needed. The establishment of specifically dedicated treatment services for persistent postsurgical pain in analogy to acute pain services has been proposed in an editorial.[16]

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Printed in the U.S.A.