Introduction

Surgery is frequently performed because a patient presents with pain. This may be acute pain, due to appendicitis, or chronic pain, because of spinal degeneration. Once the offending part of the body has been removed, or surgically corrected, the patient expects to be pain-free. Some operations are performed without a patient experiencing pain beforehand, for example a vasectomy, and these patients do not wish to suffer chronic pain as a result of such an operation. Unfortunately, whether or not an operation is performed to address pain, a certain proportion of patients who have succumbed to the scalpel, will experience chronic pain thereafter. A survey of UK pain clinics found that for patients with chronic pain, surgery was the contributory cause in 22.5% of cases, the second most common cause after degenerative disease (34.2%), and a more common cause than trauma (18.7%).

While postsurgical pain is a generic term which covers chronic pain after any operation, other pain syndromes are specific to the type of surgery, e.g. post-mastectomy, post-sternotomy or post-vasectomy pain. The aetiology of pain in these syndromes is similar, although there may be some variability, due to factors specific to the surgery, for example the type of mesh used in the repair when addressing post-inguinal herniorrhapy pain.

Definitions

Current definitions of chronic pain syndromes that occur after surgery tend to use a timescale that relates to expected “normal” duration of postoperative pain, rather than a cause, as well as a diagnosis of exclusion. For example, Macrae and Davies define postsurgical pain as "a chronic pain that has developed after a surgical procedure, of at least two months’ duration, and …other causes, e.g. malignancy or infection, have been explored and excluded." While postsurgical pain is a generic term which covers chronic pain after any operation, other pain syndromes are specific to the type of surgery, e.g. post-mastectomy, post-sternotomy or post-vasectomy pain. The aetiology of pain in these syndromes is similar, although there may be some variability, due to factors specific to the surgery, for example the type of mesh used in the repair when addressing post-inguinal herniorrhapy pain.

Incidence

It is uncertain as to whether or not the incidence of CPSP relates to the extent of tissue damage and neural injury present during surgery, but this is probably the case. Laparoscopic surgery causes less structural damage than open surgery, and generally causes less CPSP. Surgery in the thoracic region carries a high incidence of CPSP (Table I), and this is often associated with nerve injury from clips, or the use of retractors to open the chest. Limb amputations always involve transection of major nerves, and for centuries, have been known to cause CPSP often. However, relatively common minor procedures also carry a significant risk of CPSP.

Why does acute postoperative pain cause CPSP?

Tissue damage, at the site of surgery, results in the spontaneous discharge of nearby nociceptors, and an increased sensitivity to further stimuli. This is known as primary hyperalgesia. Central nervous system changes may result from this increased nociception. Sensitisation may also occur, whereby pain transmission takes place after previously non-noxious stimulation in the area surrounding the injury. This is referred to as secondary hyperalgesia, and is a major contributor to CPSP.
Where peripheral nerves are damaged by surgery, regeneration may lead to the development of nerve sprouts and neuroma formation ectopic activity, which causes further peripheral nociceptive transmission and central sensitisation. Neuropathic pain is a frequent component in many CPSP syndromes. Nociceptive impulses cause changes in the brainstem and cerebral cortex. Alterations in the connections between the spinal cord and brain result. There is an increase in the descending facilitatory influences, and a reduction in inhibitory stimuli, which causes an increase in the central transmission of pain.4

The pathological processes involved in the development of these hyperalgesic responses are gradually being clarified, including the role of the inflammatory process, which causes primary afferent nociceptor hyperexcitability. Here, the epsilon isoform of protein kinase C (PKC epsilon) has been implicated, and acts as a second messenger, subsequent to cytokines that are released in response to inflammation or environmental stress. Treatments are being developed, and directed against pro-inflammatory cytokines and PKC epsilon. (Of interest is the observation that PKC epsilon has also been linked to opioid-induced hyperalgesia, and that this can be prevented experimentally by inhibitors of PKC epsilon.5)

Central processing of peripheral pain stimuli starts at the spinal level. Spinal cord microglia become intensely activated following surgical incision, nerve injury, and chronic opioid use. These activated microglia release mediators, which lead to dorsal horn neuron excitability, partially due to suppression of inhibitory synaptic transmission. Currently, research is targeting microglial signalling, in order to prevent several chronic pain conditions, including CPSP.6

### Preventing acute postoperative pain leading to chronic postsurgical pain

There are many risk factors for CPSP6, and an awareness of these provides a focus for intervention and preventive strategies. Some risk factors cannot be changed, for example age or genetic make-up, but provide avenues for research into the cause of CPSP. Some patients are genetically less sensitive to analgesics, or are extremely fast metabolisers of analgesics (opioids and nonsteroidal anti-inflammatory drugs (NSAIDs)), and need a different dosage regimen to reach therapeutic levels.5 Older patients tend to have a lower incidence of CPSP than younger adults, but children experience less CPSP than adults,7 probably because of the relative immaturity of the child’s nervous system.8 Some patients are born more sensitive to pain, and are more likely to have CPSP. These include patients with genetic polymorphisms of catecholamine-O-methyltransferase, who have been shown to be more sensitive to pain,10 and also to have a higher incidence of CPSP.11 If these patients could be identified preoperatively, then a more aggressive perioperative pain treatment strategy might prevent the development of CPSP, although this has yet to be proven.

The first time that the majority of patients see an anaesthesiologist is when they present for an operation, already in pain, or postoperatively, when they present to the pain clinic with CPSP. This may be too late, as it is clear that preoperative pain is a major risk factor for postsurgical pain. In the case of mastectomy and amputation, experiencing pain for longer than a month before surgery was predictive of CPSP for those patients.12 The pain may be felt at the surgical site, or in a completely different part of the body.13 This concurs with studies that implicate central sensitisation as a cause of CPSP.14

Many studies have investigated whether or not treating pain before surgery reduces CPSP, particularly in the case of amputations, and it probably does. A recent 2011 study was published by Karanikolas et al. They reported that patients whose pain was relieved adequately for 48 hours preoperatively, with a patient-controlled analgesia device (opioids) or epidural, had less phantom limb pain at six
months, than those whose pain was inadequately relieved in that same preoperative period.\textsuperscript{15}

Conversely, treating preoperative pain with opioids may not always be of benefit, and this may be the case with patients in chronic pain who use opioids on a long-term basis. Studies have shown that patients who are chronically exposed to opioids preoperatively were at greater risk of experiencing CPSP.\textsuperscript{16,17} This may be due to opioid-induced hyperalgesia, and the mechanism may be similar to the acute postoperative hyperalgesia, frequently noted with the intraoperative use of remifentanil.

Preferably, chronic preoperative pain should be treated with non-opioid analgesics, to try and prevent opioid-induced hyperalgesia. Patients who are chronically exposed, preoperatively, to opioids, may benefit from perioperative drugs used to treat opioid-induced hyperalgesia. These include ketamine, NSAIDs,\textsuperscript{18} gabapentin,\textsuperscript{19} and intraoperative nitrous oxide.\textsuperscript{20}

Peripheral pain nociception is an initiator of central sensitisation, and is related to CPSP. With this in mind, considerable research has been conducted in the field of preventing afferent nociceptive information (due to surgery) from reaching the spinal cord. Amputation has been studied in this respect, particularly with regard to the use of local anaesthetic techniques, via epidural or perineural infusions. The most efficacious outcomes appear when perineural infusions are used in high concentration for several weeks, and only removed when there is no pain on temporary discontinuation of the infusion.\textsuperscript{21}

However, peripheral nociception is not the only cause of central sensitisation. The effects of other factors need to be attenuated to prevent central sensitisation and CPSP. These include those previously mentioned, for example inflammatory mediators, as well as neural ectopic activity. The main difference between pre-emptive analgesia and preventive analgesia is as follows. Pre-emptive analgesia is often administered before surgical incision, and aims to prevent early noxious impulses reaching the central nervous system and causing sensitisation. Preventive analgesia aims to prevent the effects of other factors which lead to central sensitisation throughout the perioperative period, and may be administered at any stage of the perioperative period. Preventive analgesia can be defined as “when postoperative pain and analgesic consumption are reduced relative to another treatment, a placebo treatment, or to no treatment, as long as the effect is observed at a point in time that exceeds the clinical duration of action of the target drug”, i.e. 5.5 half-lives.\textsuperscript{22} Preventive analgesia is usually given over a longer term, and may be more efficacious, for example pre-emptive antineuropathic pain medication is often shown to have less of an effect on CPSP,\textsuperscript{23} compared to preventive regimens.\textsuperscript{24,25} Preventive analgesia focuses more on the long-term benefits of using drugs to reduce CPSP, and also on functional status, which does not always correlate with pain intensity.

Higher in the central nervous system, pain perception and response play a large role in whether or not a patient develops CPSP. Preoperative psychological conditions, for example anxiety,\textsuperscript{26} and catastrophing,\textsuperscript{27} relate to acute and chronic postoperative pain. High levels of stress hormones and, in particular, catecholamines, which sensitise peripheral nociception, may be predisposing factors here.

Depressed patients, with a depressed hypothalamic-pituitary-adrenal axis, are also at greater risk of experiencing CPSP. Pain can lead to depression, but depression that manifests preoperatively results in more pain being experienced postoperatively.\textsuperscript{28,29} The question is, does treating depression that is associated with acute postoperative pain reduce the risk of CPSP? Small doses of ketamine relieved depression-like behaviour, caused by neuropathic pain, in rats, independently from its antinociceptive properties.\textsuperscript{30} Treating pain does not always improve depression.\textsuperscript{31} This implies some independence between the treatment of acute pain and depression. However, many antidepressants have a dual action, and also relieve neuropathic pain, for example amitryptilline, duloxetine, and venlafaxine. If a patient is depressed postoperatively, the use of agents with a dual antineuropathic pain and antidepressant action would be justified. Use of a combination of these agents with analgesics should be avoided, and this could precipitate the serotonergic syndrome, for example amitryptilline and pethidine.

**Conclusion**

Multimodal analgesic techniques should be used in every surgical case to provide maximal analgesia, with minimal side-effects, as this is most likely to reduce the chances of a patient developing CPSP.\textsuperscript{32} Every patient should be warned that even though the surgery may be deemed to be “minor”, whenever an incision is made, there is a chance that CPSP may develop. This may influence the patient’s decision as to whether or not to proceed with the surgery. Until there are new advances in medicine, even with multimodal analgesia, there is always a risk that CPSP will develop after surgery, but with early recognition and intervention, the consequences may be reduced.
References