When pain after surgery doesn’t go away...

Síun Burke and George D. Shorten
Department of Anaesthesia and Intensive Care Medicine, Cork University Hospital, Wilton, Cork, Ireland, and University College Cork, Cork, Ireland.

Abstract
Chronic post-surgical pain is a common, under-recognized and important clinical problem which affects millions of patients worldwide. It results from a series of neuroplastic changes associated most commonly with peripheral nerve injury at the time of surgery. Predisposing factors include the type of surgery, pre-operative and acute post-operative pain intensity, and probably psychological (e.g. pain-catastrophizing) and genetic factors [e.g. GCH1 (GTP cyclohydrolase 1) haplotype]. Preventive measures which are currently available include selection of a minimally invasive surgical technique and an aggressive multimodal perioperative analgesic regimen. Very promising therapeutic agents which target the sensitization process are currently in development.

Introduction
In 1999, Macrae and Davies [1] proposed a working definition for CPSP (chronic post-surgical pain) based on four criteria, namely: (i) pain developed after a surgical procedure; (ii) it was of at least 2 months duration; (iii) other causes for the pain had been excluded; and (iv) an attempt had been made to explore and exclude the possibility that the pain was continuing from a pre-existing problem [1]. This latter criterion is problematic. Clearly, many indications for surgery are themselves associated with inflammatory or neuropathic pain. A patient with severe peripheral vascular disease may develop ischaemic limb pain and subsequently require amputation. A patient with a prolapsed intervertebral disc may suffer from radicular pain which is refractory to medical management and undergo lumbar discectomy. In the event that these patients continue to experience pain which is similar in type and location to that present pre-operatively several months after their surgery, does that constitute CPSP? This question is important both in terms of an approach to clinical management and to standardizing clinical investigation of the problem. Macrae and Davies [1] suggest that, when a surgical procedure and the events of the perioperative period are likely to be important determinants of whether a patient has a good or bad pain outcome, then the term CPSP may be applied. Of these patients, there are two categories: (i) those in whom a characteristic pain preceded surgery, and (ii) those in whom it did not. This categorization might be useful in addressing the prevention, treatment and investigation of CPSP.

Of those patients who undergo surgery, 0.05–1.5% have persistent pain 1 year later [2], an impressive value when one considers that as many as 40 million patients undergo surgery each year in the U.S. alone [3]. Despite its prevalence, CPSP has been a largely unrecognized clinical problem prompting its description as a ‘silent epidemic’ [4]. One reason for this may be that clinical responsibility is spread over several clinical disciplines, with none accepting ‘ownership’ of the problem. Another factor may be the reluctance of patients to volunteer information on post-surgical pain as it may seem trivial when compared with the reason they initially presented for surgery.

The reported incidence of CPSP varies with the surgical procedure performed. Following inguinal hernia repair, the incidence is 0–37%, for limb amputation, it is 0–81%, for thoracotomy, it is 50%, and cholecystectomy has a CPSP incidence of 3–56%. Women who undergo breast surgery can experience persistent chest wall, breast or scar pain (11–57%), phantom breast pain (13–24%), and arm and shoulder pain (12–51%) [5]. The incidence of pain at one or more of these sites is 50% 1 year after breast surgery for cancer. The importance of the type of surgery probably relates to the risk of nerve injury, which is greater after procedures such as amputation, thoracotomy and breast surgery [6]. The severity of pre-existing and acute post-operative pain are both predictive of the likelihood of developing CPSP. Other risk factors include the presence of anxiety and pain catastrophizing as well as conditions such as irritable bowel syndrome, migraine headache, fibromyalgia and Raynaud’s disease [7]. A genetic predisposition to a poor pain outcome following lumbar discectomy has been proposed [8].

Currently, treatment of CPSP is determined by the nature of the presenting symptoms and signs. A presentation of neuropathic pain is generally limited to a neuroanatomically defined area, with associated loss of sensory and/or motor function. Often, it is treated with tricyclic antidepressants and anti-epileptics. Nociceptive pain is managed initially with analgesics such as paracetamol, non-steroidal anti-inflammatory drugs and opioids if necessary. Despite such standard medical therapy, some patients will continue to experience pain. In a study in which 43% of patients suffered post-mastectomy pain, the pain completely resolved over time in nearly 25% and decreased in an additional 34% [9]. Pain following coronary artery bypass grafting...
surgery ranges from 28 to 30% and, in contrast with post-mastectomy pain, remains stable over time [10]. A biopsychosocial approach to pain management may alleviate the daily impact of chronic pain on these patients’ lives [11].

**Mechanisms of persistent post-surgical pain**

In the perioperative period, acute tissue injury results in intense nociceptor activation. Coupled with the signals initiated by nerve injury, this can result in either reversible or sustained changes (or both) in the peripheral and central nervous systems which can amplify post-operative pain and favour its persistence. The neuroplastic changes which follow an acute inflammatory stimulus tend to be short-lived; those that follow injury to peripheral nerves are longer-lasting. The neuroplastic changes relevant to pain persistence have been classified as activity-dependent (hardly outlasting the painful stimulus), modulation (the result of post-translational changes, longer lasting but reversible) and sensitization (post-transcriptional changes resulting in very-long-lasting structural and functional changes) [12].

Peripheral sensitization results from the local action of inflammatory mediators released from injured and inflammatory cells on both transducer proteins and the terminal membrane of sensory neurons [6]. Subsequent intracellular signalling pathways result in the phosphorylation of ion channels, reducing thresholds and increasing neuronal excitability. The result is increased excitability manifest as ‘primary hyperalgesia’, an exaggerated or amplified response to a noxious stimulus. An increased expression of voltage-gated ion channels leads to abnormal pacemaker activity causing the spontaneous and repetitive firing which underlies spontaneous ongoing pain [13].

Following an acute injury, afferent sensory nerve firing and humoral signals result in both modulation and modification in the dorsal horn, including NMDA (N-methyl-D-aspartate) receptor activation. Abnormal expression of transcription factors occurs, altering the function and turnover of ion channels and receptors. Altered gene transcription in sensory neurons and in the spinal cord augments the release of excitatory transmitters and decreases inhibitory ‘tone’. The resulting central sensitization is responsible for ‘secondary hyperalgesia’, the spread of tenderness or enhanced pain sensitivity outside of an area of injury.

NO (nitric oxide) also influences the development and persistence of hyperalgesia. Proposed mechanisms for the role of NO-induced nociceptor sensitization include enhancement of the release of prostaglandin E2, inhibition of the action of an endogenous antinociceptive substance acting on peripheral nociceptors and a direct action on nociceptors [7]. Central sensitization is partially mediated by the activation of NMDA receptors with subsequent NO production [7].

The sensation of pain is subject to descending control from higher centres. Endogenous opioids, B2-endorphins, enkephalins, dynorphins, serotonin and noradrenaline all act in anti-nociceptive pathways [14]. Noradrenaline is released in the dorsal horn by descending noradrenergic axons which originate in the locus coeruleus in the brainstem and bind to α2-agonists to α2-adrenoceptors. Noradrenaline terminals are concentrated in the upper two laminae of the dorsal horn. In mice, intrathecal administration of 6-hydroxydopamine, a neurotransmitter analogue that depletes noradrenergic stores in nerve endings, dramatically lowered noradrenaline content of the spinal cord and caused hyperalgesia during a hotplate test [15]. Intrathecal noradrenaline causes analgesia in the rat. This effect is blocked by yohimbine, an α2 antagonist, indicating that the α2-adrenoceptor is the site of action of noradrenaline. Noradrenaline originating in the brainstem is inhibitory to nociceptive transmission and that spinal α2-adrenoceptors mediate inhibition of spinal nociceptive cells with ascending axons. Loss of inhibition from descending pathways dependent on monoamines such as noradrenaline, serotonin and dopamine, as well as opioids, may contribute to enhanced sensitivity after peripheral nerve injury.

On exposure to an identical surgical stimulus, why will some patients suffer persistent pain, whereas, in others, the pain resolves completely? Only a small part of the variance in pain persistence can be explained by age, severity of the injury, personality traits and social supports. These observations support a genetic basis for individual variations in pain perception and the development of CPSP [16].

**Clinical evidence: predisposing factors**

**Acute post-operative pain**

In patients who had undergone lateral thoracotomy 18 months earlier, 52% of patients reported long-term pain. Early post-operative pain was the only factor that significantly predicted long-term pain. Pain intensity 24 h after surgery, at rest and with movement, was greater among patients who subsequently developed long-term pain compared with pain-free patients [17]. In a study of 159 trauma patients undergoing elective surgery, greater pain on the fourth post-operative day was associated with persistent pain 7 months later [18].

If acute postoperative pain is a risk factor for the occurrence of CPSP, can a reduction in acute post-operative pain result in lower incidence of CPSP? In a series of studies, it was demonstrated that interventions such as intrathecal clonidine and epidural ketamine, which reduced the area of hyper-sensitivity to mechanical stimuli surrounding an abdominal wound, resulted in a lesser incidence of CPSP [12,19,20]. In a study comparing the effects of two analgesic regimens on the likelihood of developing CPSP after breast surgery, patients in the intervention group (continuous paravertebral block combined, acetaminophen and parecoxib) experienced less pain during the first 96 h post-operatively and had a lesser incidence of CPSP 10 weeks later than those who received a standard analgesic regimen [21].

Reuben et al. [22–24] have published a series of studies on perioperative interventions to decrease the incidence of CPSP. In patients undergoing cervical spine fusion surgery, low-dose...
morpheine applied to the harvest graft site reduced acute pain from 4 to 24 h post-operatively and reduced donor site pain 1 year after surgery when compared with controls [22]. Patients who received a combination of acetaminophen and celecoxib before and for 14 days after anterior cruciate ligament surgery had less pain, fewer patellofemoral complications and a greater level of activity at 6 months than those who received acetaminophen alone [23]. The perioperative administration of venlafaxine, a 5-hydroxytryptamine (serotonin) and noradrenaline re-uptake inhibitor, significantly decreased the incidence of CPSP following breast cancer surgery [24].

**Patient education**

Information influences the pain experience after surgery. In one study, the provision of preoperative information resulted in post-operative pain declining more rapidly, lower pre-operative anxiety and more satisfaction with post-operative pain management [25].

A greater awareness of the existence of CPSP will improve its detection rate and prompt physicians to disclose accurate data about the incidence of pain after certain operations.

**Genetic factors**

Inbred rodent strain and human twin studies indicate that the risk of developing chronic pain may be genetically determined. Of the several hundred genes regulated in the DRG (dorsal root ganglion) following sciatic nerve injury, Tegeder et al. [8] identified up-regulation of two of the three enzymes in the synthesis cascade of BH4 (tetrahydrobiopterin), including the rate-limiting enzyme GCH1 (GTP cyclohydrolase 1). BH4 is essential for catecholamine, 5-hydroxytryptamine and NO synthesis and is increased in peripheral inflammation and injury owing to enhanced GCH1 activity. Inhibiting BH4 synthesis in rats attenuated neuropathic and inflammatory pain. In humans, a haplotype of GCH1 (population frequency 15.4%) was significantly associated with lower degrees of persistent pain following lumbar discectomy [8].

**Psychological factors**

A prospective study of 295 women examined the effect of pre-surgical psychological distress and somatic preoccupation in predicting persistent pain after post-mastectomy reconstructive surgery. At 1- and 2-year follow-up, affective distress, depressive and anxiety symptoms and somatization held significant association with abdominal and back pain. For breast pain, all of the psychological measures predicted more severe pain at 1 year, but none retained significant association at year 2 [26].

**Prevention**

Although the evidence to date is limited, it is likely that the use of minimally invasive surgical techniques will decrease the incidence of CPSP. Multimodal analgesia refers to the technique of combining multiple modalities of pain relief to provide more effective analgesia and a lesser incidence of adverse effects. Providing optimal dynamic pain relief with minimal adverse effects may prevent central sensitization and consequently CPSP. Although opioids have potent analgesic effects for spontaneous pain, they may be inadequate for the treatment of movement evoked pain and have minimal effects on modifying neuronal plasticity and reversing established central sensitization [27]. In contrast, local anaesthetic techniques, COX2 (cyclo-oxygenase 2) inhibitors, α2-adrenoreceptor agonists, α2δ ligands and NMDA receptor antagonists may be important for controlling movement-evoked pain and preventing the development of central sensitization [28,29].

**The future**

The use of minimally invasive surgical techniques are likely to be effective by decreasing the likelihood of nerve injury and by lessening the associated inflammatory response. Long-term neural blockade, by preventing afferent nerve firing from the site of injury, may prevent activity related changes in the central nervous system [6]. Paravertebral block for breast surgery decreases the incidence of pain symptoms, the intensity of motion-related pain and the intensity of pain at rest 12 months post-operatively [30]. Multimodal analgesia with gabapentin and topical application of EMLA (eutectic mixture of local anaesthetic) decreases post-operative analgesic requirements and the incidence and intensity of CPSP 3 months after breast surgery [31]. Multimodal analgesia using a continuous paravertebral block and regular acetaminophen and parecoxib decreases the incidence of CPSP 10 weeks after breast surgery [21].

**GDNF (glial-cell-line-derived neurotrophic factor)**

GDNF both prevents and reverses sensory abnormalities that develop in neuropathic pain models [32]. GDNF promotes survival of some sensory axons during early development and has a neuroprotective effect on damaged sensory neurons in adults [33]. These observations indicate a potential role for GDNF in the prevention and treatment of CPSP.

**NK-1 (neurokinin 1) receptor antagonist**

Mice in which the gene for the NK-1 (substance P) receptor is absent show deficiencies in spinal ‘wind-up’ [34]. In animal models, antagonism of the NK-1 receptor demonstrates substantial evidence of antinociception, especially in inflammatory hyperalgesia. Despite this evidence, the long-acting orally active NK-1 receptor antagonist aprepitant was ineffective in reducing an area of electrically evoked hyperalgesia in human volunteers; in a dental pain model, pre-operative aprepitant failed to demonstrate effective analgesia [35,36].

**Na\(_v\)1.3/Na\(_v\)1.7/Na\(_v\)1.8/Na\(_v\)1.9 blockade**

In neuropathic pain states, the expression of certain channels is modified; these changes underlie the plasticity of responses that occur to generate inappropriate pain signals from normally trivial inputs. Pain is modulated by a subset of the voltage-gated sodium channels, including Na\(_v\)1.3, Na\(_v\)1.7, Na\(_v\)1.8 and Na\(_v\)1.9 [37].
Phenotyping of mice carrying a nociceptor-specific deletion of the Na$_{1.7}$ gene has provided evidence for a role of this sodium channel subtype in mediating inflammatory pain signalling [38]. Na$_{1.8}$-null mutant mice displayed reduced sensitivity to inflammatory hyperalgesia [39]. Finally, Na$_{1.9}$-null mutant mice provide evidence that the Na$_{1.9}$ subtype also contributes to inflammatory pain signalling [40].

Systemic delivery of A-803467 [5-(4-chlorophenyl-N-(3,5-dimethoxyphenyl)furan-2-carboxamide], a selective Na$_{1.8}$ sodium channel blocker reduces behavioural measures of chronic pain. The effects of A-803467 on evoked and spontaneous firing of WDR (wide dynamic range) neurons were measured in uninjured and rats with spinal nerve ligation. Systemic administration of A-803467 reduced evoked WDR neuron firing, whereas intraspinal administration reduced both evoked and spontaneous WDR neuron firing [41].

Purinergic receptor antagonists
The purinergic receptors P1, P2X and P2Y appear to be involved in nociceptive pathways. P2X$_3$ receptors on spinal microglia have been implicated in allodynia. In the DRG, the presence of P2X$_3$ mRNA-labelled neurons is increased 3 days after peripheral nerve injury [42]. Mechanical allodynia caused by surgical injury may involve local release of ATP and its action on P2X nociceptive receptors [43]. Involvement of P2X$_3$ and P2X$_2$ receptors in neuropathic pain in the mouse chronic constriction injury model has also been demonstrated [44]. Agents that block P2 receptors may be useful as preemptive antiallogenic drugs for alleviating the post-operative pain syndrome in humans. Inflammatory mediators such as substance P and bradykinin sensitize nociception through phosphorylation of P2X$_3$ and P2X$_2$, ion channels or associated proteins [45]. This might contribute to the increase in purinergic nociception in inflammatory conditions.

$\alpha_2\delta$ calcium channel blockers
The anti-epileptic drugs gabapentin and pregabalin are efficacious in the treatment of neuropathic pain associated with diabetic peripheral neuropathy and post-herpetic neuralgia [46]. Pregabalin binds to the $\alpha_2\delta$ subunit of calcium channels, reducing depolarization-induced calcium influx and thereby decreasing the release of excitatory neurotransmitters, including glutamate, noradrenaline and substance P. A single dose of gabapentin administered to patients before mastectomy decreases post-operative morphine consumption and pain during movement [47]. Gabapentin, as part of a multimodal analgesic regimen, decreased the incidence of CPSP at 10 weeks after breast surgery [21]. A recent randomized controlled clinical trial within our department demonstrated acute antihyperalgesia and an improved pain and functional outcome in patients who received perioperative pregabalin while undergoing lumbar disc surgery. The visual analogue scale for pain on movement at 3 months was significantly reduced in the pregabalin-treated group (9.61 ± 2.594 compared with 21.35 ± 4.852; $P = 0.023$). The percentage reduction from baseline of the Roland–Morris disability score was also significantly better in the pregabalin-treated group (79.97 ± 4.76 compared with 64.7 ± 5.98; $P = 0.033$).

Free-radical scavengers: vitamin C, NAC (N-acetyl-L-cysteine) and mannitol
Free radicals promote inflammation and systemic and local tissue injuries. Free-radical scavengers are neuroprotective against excitotoxic insults. Therefore free-radical scavengers may be analgesic for pain induced by excitotoxicity or inflammation. Vitamin C, at a daily dose of 500 mg for 50 days, reduces the prevalence of CRPS (complex regional pain syndrome) after wrist fractures [48].

Intraperitoneal administration of NAC resulted in significant reduction of hyperalgesia in CCI (chronic constriction injury)-induced neuropathic rats [49]. However, a recent study on mannitol in 41 CRPS patients concluded that intravenous administration of 10% mannitol is no more effective than placebo in reducing complaints for CRPS I [50].

In conclusion, CPSP is an established clinical entity and its incidence varies with surgical procedures. Optimal perioperative management to reduce the incidence of CPSP requires: refinement of minimally invasive surgical techniques, increased utilization of sensory blockade and the enhanced use of multimodal perioperative analgesics.

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