Chronic post-surgical pain

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Chronic post-surgical pain (CPSP) is one of the most common and serious complications after surgery. There is no universally agreed definition of CPSP; however, the working definition proposed by Macrae and Davies is commonly used (Fig. 1). CPSP is associated with increased analgesic use, restriction of activities of daily living, significant effects on quality of life, and increased health-care utilization. More than 4 million people undergo surgery every year in the UK, so CPSP poses a significant economic and health-care burden. Not all studies are consistent about the incidence of CPSP; there are wide variations between different surgical procedures (Table 1). Some of this variability is likely to result from lack of clarity in the definition of CPSP, small sample sizes, poor questionnaire response rates, and selection bias.

Nerve injury during surgery has been implicated in the development of CPSP; some (but not all) patients with CPSP have neuropathic pain. Inflammatory and immune reactions after damage to axons result in release of neurotransmitters that act locally and in the spinal cord to produce hypersensitivity and ectopic neural activity; this contributes to central sensitization (Fig. 2). Central sensitization occurs when repetitive nociceptive stimuli result in altered dorsal horn activity and amplification of sensory flow; this can lead to persistent nervous system changes, for example, death of inhibitory neurones, their replacement with excitatory afferent neurones, and microglial activation. These changes lead to evoked and spontaneous symptoms associated with neuropathic pain, for example, allodynia and hyperalgesia. CPSP is reported in more than 50% of patients who have surgery associated with nerve and tissue damage, for example, mastectomy, thoracotomy, and amputation. Despite this, there is no simple relationship between nerve injury during surgery and the development of CPSP. There is no association between intercostal nerve damage assessed at the time of thoracotomy by nerve conduction studies and the development of chronic pain 3 months later. Paradoxically, rib resection, which results in more intercostal nerve damage, is associated with a reduced incidence of post-thoracotomy neuralgia.

Similarly, although damage to the intercostobrachial nerve has been implicated in the development of CPSP after mastectomy, many patients with objective signs of nerve injury (such as numbness) do not develop chronic pain. In addition, other surgical procedures associated with nerve damage, not all patients with CPSP have neuropathic pain, for example, among thoracic surgery patients with CPSP, only half had significant neuropathic symptoms identified by a validated questionnaire. Patients with chronic pain after surgical procedures such as hip arthroplasty and hysterectomy do not demonstrate sensory loss, suggesting that mechanisms other than nerve injury are responsible for ongoing pain in these patients.

Therefore, any link between nerve damage during surgery and the development of CPSP is complicated. Not all patients with nerve damage develop CPSP, and those who do develop CPSP do not necessarily have neuropathic pain. Some operations not associated with nerve damage can result in CPSP. Although the mechanisms behind the development of CPSP have yet to be fully elucidated, a number of risk factors have been identified. As our understanding of the pathophysiology, risk factors, and prevention of CPSP expands, the traditional focus of the anaesthetist on managing acute perioperative pain should include identifying and managing patients at risk of developing CPSP.

Risk factors for CPSP

A number of pre-, intra-, and postoperative risk factors have been identified for the development of CPSP. The existence and intensity of preoperative pain is a risk factor for the development of CPSP after hernia repair, thoracotomy, amputation, and mastectomy; for the
latter two procedures, continuous preoperative pain for more than 1 month predicts CPSP. Increasing age is inversely related to the development of CPSP; the probability of developing CPSP after breast cancer surgery decreases by 5% for each yearly increase in the patient’s age. Genetic susceptibility is likely to play a role in the development of CPSP. There are several examples of this, for example, single nucleotide polymorphisms coding for the catecho-O-methyl-transferase enzyme are associated with the development of chronic pain conditions, for example, temporo-mandibular joint disorder. Genetic variability in the expression of enzymes responsible for neurotransmitter synthesis in the dorsal root ganglion is associated with persistent pain after lumbar discectomy. Psychosocial factors have an important effect on chronic pain; the impact of preoperative cognitive and behavioural traits on the development of CPSP has yet to be fully explored. However, preoperative psychological measures have been shown to predict pain severity a year after breast surgery, and fear of surgery is associated with worse pain and quality of life outcomes.

Intraoperative factors influence the development of CPSP. Longer (and by implication more complicated) operations are associated with more chronic pain. Laparoscopic surgical approaches result in less chronic pain after hernia repair and cholecystectomy. Repeat surgery for hernia repair has a higher incidence of moderate to severe pain intensity at 12 months compared with primary repair.

Postoperative factors also influence the development of CPSP. Adjuvant interventions such as radiotherapy increase the risk of developing chronic pain after surgery. The severity of postoperative pain significantly predicts the development of CPSP, supporting the hypothesis that repetitive nociceptive stimulation during the perioperative period results in nervous system changes such as central sensitization.

Although identification of risk factors for the development of CPSP is important, their validity in predicting CPSP for individuals is not clear. However, the response of patients to experimental pain has predictive qualities when applied to the acute pain experience after knee surgery and Caesarean section. Evaluation of endogenous analgesic systems using diffuse noxious inhibitory control has demonstrated some predictors for development of CPSP.

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**Fig 2** Cascade of events after peripheral nervous system lesion resulting in central sensitization. After peripheral nerve injury, increased sodium channel expression on sensitized primary afferents leads to spontaneous activity with increased glutamate release from nerve endings. This excess of glutamate acts on glutamate receptors triggering intracellular changes. These changes contribute to sustained central sensitization, with increased spontaneous impulse discharges, reduced thresholds, increased response to peripheral stimuli, and expanded receptive fields of central neurons. Reprinted by permission from Macmillan Publishers Ltd, copyright 2006.

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**Table 1** Procedure-specific incidence of CPSP. Reprinted with permission from Elsevier

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Incidence of chronic pain (%)</th>
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<tbody>
<tr>
<td>Amputation</td>
<td>30–85</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>5–67</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>11–57</td>
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<tr>
<td>Inguinal hernia repair</td>
<td>0–63</td>
</tr>
<tr>
<td>Sternotomy</td>
<td>28–56</td>
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<tr>
<td>Cholecystectomy</td>
<td>3–56</td>
</tr>
<tr>
<td>Knee arthroplasty</td>
<td>19–43</td>
</tr>
<tr>
<td>Breast augmentation</td>
<td>13–38</td>
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<tr>
<td>Vasectomy</td>
<td>0–37</td>
</tr>
<tr>
<td>Radical prostatectomy</td>
<td>35</td>
</tr>
<tr>
<td>Gynaecological laparotomy</td>
<td>32</td>
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<tr>
<td>Iliac crest bone harvest site</td>
<td>30</td>
</tr>
<tr>
<td>Hip arthroplasty</td>
<td>28</td>
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<tr>
<td>Saphenectomy</td>
<td>27</td>
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<tr>
<td>Hysterectomy</td>
<td>25</td>
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<tr>
<td>Craniotomy</td>
<td>6–23</td>
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<tr>
<td>Rectal amputation</td>
<td>12–18</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>12</td>
</tr>
<tr>
<td>Dental surgery</td>
<td>5–13</td>
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chronic pain after thoracic surgery, although interestingly showed no correlation with the acute pain experience.\textsuperscript{7}

**Preventative anaesthetic techniques**

Pre-emptive regional analgesia (regional analgesia commenced before surgical incision with the aim of being more effective than the same treatment started after surgery) has conferred little benefit for preventing CPSP. A meta-analysis of pre-emptive epidural compared with epidural commenced after completion of thoracic surgery did not affect development of CPSP; this did not take into account the effects of continuing the epidural after surgery.\textsuperscript{8}

In contrast, preventative regional analgesia has demonstrated some promising results (although data are limited). Preventative analgesia is given in the perioperative period, but has an effect that extends beyond the duration of the drugs used. Epidural analgesia when commenced before surgery and continued into the postoperative period reduces the incidence of CPSP in patients undergoing thoracotomy and laparotomy. Similarly, paravertebral block initiated before incision and continued into the postoperative period reduces the incidence of CPSP in thoracic and breast cancer surgery patients. It may be that establishing sufficient afferent block before the surgical incision and continuing this well into the postoperative period reduces the nociceptive barrage that results in central sensitization.

The preventative effects of perioperative gabapentin have been studied, but with inconclusive results. Gabapentin failed to reduce the incidence of chronic pain after amputation when given during the perioperative period and for 30 days afterwards. In contrast, when used in conjunction with local anesthetics, perioperative gabapentin reduced the incidence of chronic pain in breast cancer surgery patients. Perioperative i.v. ketamine infusion has been used to prevent development of CPSP in patients undergoing mastectomy, thoracotomy, and rectal cancer surgery. Clonidine, when used in conjunction with local anesthetics as a regional anaesthetic technique, may reduce the incidence of CPSP. There are limited data to suggest that multimodal analgesic techniques (such as a combination of Local anaesthesia and gabapentin or intra-articular bupivacaine, morphine, and clonidine) may help reduce CPSP.

Some patients develop neuropathic pain symptoms in the immediate postoperative period and anti-neuropathic medications such as gabapentin are increasingly being used by the acute pain service. It is not known whether treating neuropathic pain in the postoperative setting reduces the development of chronic neuropathic pain after surgery.

**Future developments**

Spinal cord microglial cells modulate synaptic function and neuronal excitability; activation of these cells has an important role in the development of neuropathic pain after peripheral nerve injury.\textsuperscript{9} Minocycline is a tetracycline antibiotic with anti-inflammatory properties distinct from its antimicrobial activity. It has been shown to inhibit the activation of microglial cells. Animal studies have shown that administration before nerve injury attenuates the development of pain hypersensitivity. Other potential targets include the spinal cord and dorsal root ganglion purinergic receptors; these receptors have been implicated in the development of neuropathic pain in animal models. Nerve injury resulting in allodynia was associated with the release of ATP that acts at purinergic nociceptive receptors. Block of these receptors may have a preventative role in the development of pain after nerve injury. Altered expression of sodium channels (such as Na\textsubscript{+}, 1.8) occurs in animal models of chronic pain and selective sodium channel blockers have reduced behavioural measures of chronic pain in rats.

**Conclusion**

CPSP is a common and important problem. Although research is limited, it is likely that perioperative anaesthetic techniques may have a role in reducing its prevalence. Considering the multi-factorial pathogenesis of chronic pain, it is likely that a multi-modal approach to preventative analgesia and attention to psychosocial risk factors is most likely to influence the development of CPSP.

**References**


Please see multiple choice questions 8–10