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Review Article

Preventing chronic postoperative pain

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Summary

Chronic postoperative pain is common. Nerve injury and inflammation promote chronic pain, the risk of which is influenced by patient factors, including psychological characteristics. Interventional trials to prevent chronic postoperative pain have been underpowered with inadequate patient follow-up. Ketamine may reduce chronic postoperative pain, although the optimum treatment duration and dose for different operations have yet to be identified. The evidence for gabapentin and pregabalin is encouraging but weak; further work is needed before these drugs can be recommended for the prevention of chronic pain. Regional techniques reduce the rates of chronic pain after thoracotomy and breast cancer surgery. Nerve-sparing surgical techniques may be of benefit, although nerve injury is not necessary or sufficient for chronic pain to develop.

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Introduction

Approximately one in four patients identifies surgery as the cause of their chronic pain [1]. The rate of chronic postoperative pain varies with the type of operation. Chronic pain develops in one in two patients who have leg amputations, breast cancer surgery and thoracotomy [2–4]. The chronic pain rate is 1 in 2.5 after coronary artery bypass surgery, 1 in 5 after total knee arthroplasty, 1 in 6 after inguinal hernia repair and 1 in 10 after caesarean section [5–8]. The scale of this problem is considerable: for instance, each year approximately 100 000 hernias are repaired in the UK, causing chronic pain in about 17 000 patients. The pain is severe and disabling for 1 in 10 patients with chronic pain [9]. Chronic postoperative pain often makes life worse, impairing function and causing distress. Chronic pain is difficult to treat and is often permanent. For this reason, efforts to prevent the development of chronic pain after surgery are vital [10].

The following criteria have been suggested for the diagnosis of chronic postoperative pain [11]:

- The pain developed after a surgical procedure
- The pain is of at least two months' duration, although this has been criticised as too short a time for postoperative inflammation to have resolved [12]
- Other causes of pain have been excluded, such as malignancy or chronic infection

This review will discuss the pathogenic mechanisms thought to contribute to persistent postoperative pain, peri-operative preventative strategies with the potential to reduce the risk of chronic pain, the impact of psychosocial factors and the potential value of genetic analysis to stratify risk and treatment for the individual.

Pathophysiology

Acute postoperative pain is a result of noxious stimulation of skin, subcutaneous tissues, viscera and

neural structures [13]. Nociception is a protective process that helps prevent further tissue damage by triggering reflex withdrawal responses and modification of behaviour to avoid injury [14]. Inflammatory mediators released at the site of tissue injury cause a reduction in the threshold of afferent nerve endings (peripheral sensitisation) so that a lesser stimulus is required to activate nociceptors, hence producing hypersensitivity at the site of inflammation [9]. The rates of ectopic discharges increase from injured and nearby uninjured nerves, possibly due to increased expression of voltage-gated sodium channels [15]. The barrage of afferent input from the injury site causes central neurons to become hyperexcitable, leading to an exaggerated response by these to normal sensory inputs [14]. These are usually short-lived, activity-dependent processes, mediated largely by glutamate via the N-methyl-D-aspartate (NMDA) receptor, that resolve with injury resolution. Patients experience spontaneous pain, allodynia and hyperalgesia at, and adjacent to, the site of injury [13].

The mechanisms that mediate the transition from this acute, adaptive postoperative pain to chronic, maladaptive pain are not fully understood, although nerve injury and ongoing inflammation play important roles [9]. Persistent pain following surgery can have neuropathic characteristics [16, 17], and many of the operations associated with persistent pain, such as thoracotomy, breast surgery and amputation, involve major nerves in the surgical field. Major nerve injury accompanies stretching or crushing as well as transection [18]. However, intra-operative nerve transection does not inevitably result in neuropathic pain, and avoiding nerve transection does not necessarily prevent chronic pain [19]. Risk factors for persistent postoperative pain, other than nerve injury and ongoing inflammation, include pre-operative pain, younger age, female sex, genetic factors and psychological vulnerability [18].

Acute pain management and preventive analgesia

The risk of chronic pain has been consistently associated with the severity of acute postoperative pain [8, 17, 20], possibly because of a shared predisposition to both. However, the relationship may be causal, leading to the hypothesis that reducing acute postoperative pain reduces the risk of chronic pain [18]. Indeed, peri-operative analgesics that have 'antihyperalgesic' actions appear to reduce central sensitisation and hence the progression to chronic pain [13].

The site, timing and intensity of surgical damage are predictable. An analgesic regimen can be designed to anticipate, prevent or modify the nociceptive barrage, thereby preventing central sensitisation. Pre-emptive analgesia, defined as analgesia administered before the surgical incision, is intended to attenuate the physiological sequelae of nociception [13]. However, there is a lack of evidence for the benefit of pre-emptive regional or systemic analgesia on acute postoperative pain, and there are insufficient data to draw conclusions on the impact of pre-incisional or postincisional analgesia on chronic pain [21].

While pre-emptive analgesia is administered *before* the surgical incision to target the immediate peri-operative period, the intention with 'preventive' analgesia is to block nociceptive signals *from* the time of the initial surgical stimulus until final wound healing, so blocking central sensitisation [13]. Preventive analgesia provides analgesia beyond the expected duration for that agent, which has been defined as more than 5.5 half-lives [18]. The emphasis with preventive analgesia is on adequacy and duration of the analgesic intervention [13]. Drugs such as ketamine, gabapentin and pregabalin have been investigated as anti-hyperalgesics, because they have mechanisms of action affecting the central nervous system.

Factors influencing chronic postoperative pain

Drugs

Ketamine

The mechanisms of ketamine's anti-nociceptive actions includes activation of descending inhibitory monoaminergic pain pathways and antagonism of NMDA receptors [22], its action on the latter having originally stimulated interest in its anti-hyperalgesic properties.

Ketamine may prevent hyperalgesia at subanaesthetic doses [23]. A 0.5 $mg.kg^{-1}$ ketamine bolus, followed by an intra-operative infusion at 0.25 $mg.kg^{-1}.h^{-1}$, reduced surgical site pain two weeks after anterior resection and at one and six postoperative months, compared with those receiving a lower

dose of intravenous or epidural ketamine [23]. Early postoperative analgesia was also better, and the area of mechanical hyperalgesia around the wound was reduced.

Systematic review and meta-analysis of randomised controlled trials suggest that systemically administered ketamine reduces chronic postoperative pain [24]. Trials were undertaken in a range of surgeries and ketamine was administered using a variety of regimens, but the majority involved a pre-incisional loading dose of 0.15–1.00 $mg.kg^{-1}$, with additional intra-operative infusions. Further large-scale studies are required to confirm these findings, as well as to determine which subgroups benefit and the optimum dose and duration of therapy [24].

Gabapentinoids

Gabapentin and pregabalin are structurally similar to gamma-aminobutyric acid (GABA), although neither has any activity at GABA receptors. These drugs bind to the alpha-2-delta subunit of pre-synaptic voltage-gated calcium channels, inhibiting calcium influx and attenuating glutamate release in the nociceptive pathways, so reducing pain transmission and central sensitisation [25].

Gabapentin and pregabalin reduce immediate postoperative pain and opioid consumption [25, 26]. Long-term effects on postoperative pain are equivocal [24, 26, 27] (Table 1). One systematic review concluded that gabapentin and pregabalin reduced pain 3–6 months after surgery [27]. Of eight gabapentin trials examined, four reported a reduction in pain or analgesic use at long-term follow-up [29–31, 42], and four found no benefit [28, 32, 33, 43]. In one study, the combination of gabapentin with a topical and infiltrated local anaesthetic reduced pain, therefore the contribution of gabapentin alone was unknown [42]. A Cochrane review of 10 trials of gabapentin [2, 28–35, 43], including one excluded by the other systematic review, and five trials of pregabalin [36–39, 41] concluded there was no evidence of benefit for either [24].

The most recent systematic review suggested that pregabalin reduced neuropathic pain [26]. Evidence of benefit was largely restricted to one well-conducted trial of pregabalin for total knee arthroplasty [28]: pregabalin 300 mg was given 1–2 h before surgery and 150 mg was given twice daily for 10 postoperative days, after which 50 mg was given twice daily for four more days. Pregabalin reduced the rates of neuropathic pain at three and six postoperative months compared with placebo, but increased sedation and confusion for the first postoperative day, without affecting hospital stay.

The sample sizes in the majority of trials of gabapentin, pregabalin and ketamine have been small, powered to detect differences in outcomes other than chronic pain: future trials need to recruit sufficient participants to detect statistically significant, clinically important effects of drugs on chronic pain [24]. Future trials should compare the effects of the different doses and durations of therapy used in published trials. For example, reported pre-operative doses of gabapentin have ranged from 300 to 1200 $mg.day^{-1}$ and have been administered as single doses or for courses lasting up to 30 postoperative days. The effects and side-effects of these drugs and their interactions should be assessed using standardised measures of pain at agreed time points [24]. Gabapentin and pregabalin can cause sedation, dizziness and visual disturbance [26]. Ketamine can cause psychotropic effects and might only benefit patients with the highest risk of developing chronic postoperative pain.

It is unlikely that a single drug will be sufficient to block central sensitisation. Prolonged multimodal therapy, involving anti-hyperalgesic drugs with effects on central sensitisation, combined with regional anaesthesia and nerve-sparing surgical techniques are likely to be most beneficial [13].

Blockade

Effective regional anaesthesia may prevent central sensitisation by blocking nociceptive input into the spinal cord [19]. Systematic reviews of regional anaesthesia have concluded that epidural anaesthesia and paravertebral blocks reduce the risk of persistent pain six months after open thoracotomy and breast cancer surgery, respectively, preventing persistent pain for one in four patients treated [44]. These findings are interesting also in view of the apparent beneficial effect of regional anaesthesia in reducing tumour recurrence [45]. Data for paravertebral blockade were pooled from two breast cancer studies of 89 women in whom

Table 1 Randomised, double-blind, placebo-controlled trials examining the chronic postoperative analgesic effects of gabapentin and pregabalin.

Study	Intervention	N	Operation	Anaesthetic	Outcome
Fassoulaki et al. [28]	Gabapentin 400 mg or mexiletine 200 mg pre-op' then postop' tds for 10 days	75	Modified radical mastectomy or lumpectomy with axillary dissection	General	No effect on pain or analgesic use at 3 months for either intervention, but more burning pain in control group
Nikolajsen et al. [2]	Gabapentin titrated to 2400 mg.day^{-1} postop' 30 days	46	Lower limb amputation	Epidural, with or without general or spinal	No effect on stump or phantom pain at 3 and 6 months
Brogly et al. [29]	Gabapentin 1200 mg pre-op'	50	Total or partial thyroidectomy	General + superficial cervical plexus block	Less neuropathic pain at 6 months
Sen et al. [30]	Gabapentin 1200 mg pre-op' or intravenous ketamine 0.3 mg.kg^{-1} pre-op' plus 0.05 mg.kg^{-1}.h^{-1} intra-op'	60	Abdominal hysterectomy	General	Less incisional pain at 1, 3 and 6 months compared with ketamine and control
Sen et al. [31]	Gabapentin 1200 mg pre-op'	60	Inguinal herniorraphy	Spinal	Less pain at 1, 3 and 6 months
Amr et al. [32]	Gabapentin 300 mg or venlafaxine 37.5 mg pre-op' then postop' for 10 days	150	Partial or radical mastectomy with axillary dissection	General	Venlafaxine reduced pain at 6 months but more burning pain in control group
Moore et al. [33]	Gabapentin 600 mg pre-op'	46	Caesarean section	Spinal	No difference in pain or abnormal sensation at 3 months
Ucak et al. [34]	Gabapentin 1200 mg pre-op' then postop' for 2 days	40	Coronary artery bypass grafting	General	No difference in pain at 3 months
Kinney et al. [35]	Gabapentin 600 mg pre-op'	120	Thoracotomy	Epidural + general	No difference in pain at 3 months
Kim et al. [36]	Pregabalin 150 mg pre-op' then 12 h later	99	Endoscopic thyroidectomy	General	No difference in pain at 3 months
Burke et al. [37]	Pregabalin 300 mg pre-op' then 150 mg postop' at 12 h and 24 h	40	Lumbar discectomy	General	Less pain at 3 months
Buvanendran et al. [38]	Pregabalin 300 mg pre-op' then postop' 50-150 mg bd for 14 days	240	Total knee arthroplasty	Combined spinal epidural + sedation	Decreased neuropathic pain at 3 and 6 months
Pesonen et al. [39]	Pregabalin 150 mg pre-op' then postop' 75 mg bd for 5 days	70	Coronary artery bypass grafting or single valve repair or replacement	General	Less pain on movement at 3 months
Fassoulaki et al. [40]	Pregabalin 150 mg pre-op' then postop' for 5 days	80	Abdominal hysterectomy or myomectomy	General	No effect on incidence of pain at 3 months
Giansello et al. [41]	Pregabalin 300 mg pre-op' then postop' 150 mg bd for 2 days	60	Decompressive lumbar laminectomy with spinal fusion	General	No difference in pain at 3 months and 1 year

pre-incisional, single shot paravertebral blocks were combined with general anaesthesia [46, 47]. Heterogeneity of the other studies in the systematic review precluded further meta-analyses by surgical subgroup [44], but randomised controlled trials have shown long-term analgesic benefits of regional anaesthesia following laparotomy [48], caesarean section [49, 50] and cardiac surgery [51], but not gynaecological laparotomy,

herniorrhaphy and breast cancer surgery (wound infiltration and intercostal nerve block) [52–54].

Surgery

Techniques that reduce intra-operative nerve injury might reduce chronic postoperative pain. For example, the rates of persistent pain and numbness after hernia repair are less after laparoscopic than open surgery, which is thought to be due to less nerve damage occurring during the former [7, 9]. The high rate of chronic pain after thoracotomy may be due to intercostal nerve injury caused by rib retractors. However, trials have not shown that pain is less after video-assisted thoracic surgery compared with open surgery, even though the former should cause less nerve trauma [16]. The surgeon performing the operation has been shown to significantly influence the likelihood of a patient developing chronic postoperative pain. Fewer women whose surgeons operate in high volume units have chronic pain after breast surgery, possibly due to less damage of the intercostobrachial nerve [55]. This may relate to the surgical technique, anaesthesia, peri-operative analgesia or psychological factors [16]. Neurophysiological studies have demonstrated that nerves are injured in patients with and without post-thoracotomy pain, indicating that factors other than nerve injury are important [56]. Operations longer than three hours are associated with an increased rate of chronic pain, although this association may be caused by more complex pathology and intra-operative tissue damage [57].

Psychology

Two systematic reviews have found that catastrophising pain, anxiety, depression, stress and late return to work are associated with chronic postsurgical pain [58, 59]. Fear of the long-term consequences of surgery is associated with impaired long-term physical function [60].

Chronic pain develops more often in people who catastrophise, whilst general anxiety is an inconsistent factor [58]. 'Catastrophising' pain is characterised by magnification of the value of its threat, rumination on pain, and/or feelings of helplessness in the context of pain [61]. Catastrophising is more marked among patients undergoing musculoskeletal surgery [58] and is the strongest predictor of persistent pain in patients undergoing total knee arthroplasty, an operation after which one in five patients suffers persistent pain [6].

Pre-operative screening may identify patients at increased risk of chronic pain and could facilitate targeted peri-operative interventions to reduce pain and to increase patients' abilities to cope with pain. It is also important that patients are educated about the procedure and expected outcomes, enabling patient participation in the decision-making process [6]. When patients are given information about what they should expect to feel after surgery, in addition to procedural information, they experience less pain and distress than if either type of information is given alone [62]. Ensuring consistency of information may be a key factor in reducing catastrophising behaviours [6]. Further research into the peri-operative use of psychoactive medications, such as anxiolytics, may also reveal long-term benefits of a pharmacological strategy to reduce the rate of chronic pain [63].

Genes

It is likely that genetic variation contributes to the phenotypic variation in acute and chronic postoperative pain after the same operation [64]. Animal and human studies suggest that genes account for 30–70% of the variation in chronic pain [65].

Genes have been identified that are responsible for inherited abnormalities in pain processing [65]. The hereditary sensory and autonomic neuropathies (HSAN 1-4), for example, are a group of syndromes resulting from single gene mutations. Pain perception and responses are markedly diminished or absent and affected individuals often accumulate painless injuries [65]. There are also conditions associated with enhanced pain sensitivity. For example, the neuropathic pain condition, erythromelalgia, is associated with a mutation in the SCN9A gene that reduces the electrical activation threshold of the $Na_v1.7$ voltage-gated sodium channel [65]. The association of pathological conditions with genetic abnormalities contributes to our understanding of pain processing. However, this knowledge has yet to benefit patients with chronic pain [65].

No single gene is responsible for chronic pain after surgery, but the interaction of multiple genes and the environment is likely to be important [64]. It is possible

that there are different genes that confer specific vulnerability to different aspects of pain, for example frequency of painful episodes, type of pain (e.g. burning, electric shock-like) or spread of pain around the surgical site [18]. Recent studies have identified a few candidate genes for chronic postoperative pain [64]. Susceptibility to chronic pain following nerve injury during breast surgery is associated with polymorphisms in CACNG2, which encodes the protein 'stargazin' that traffics glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors [66].

Genes are also responsible for many aspects of analgesic efficacy. Polymorphisms in the CYP2D6 gene affect the O-demethylation of codeine and other weak opioids to more potent metabolites – poor metabolisers experience less analgesia. Similarly, single nucleotide polymorphisms in the mu-receptor are associated with increased morphine requirements [67]. It might be hoped that our understanding of pharmacogenomics will develop sufficiently to allow the formulation of patient-specific analgesic regimens for those at high risk of persistent postoperative pain or to treat those with established chronic pain. It is clear that there is still a long way to go before it will be possible to use a patient's genetic fingerprint to identify their risk of chronic pain after surgery. Nevertheless, this remains an essential line of investigation if we are to achieve the goal of individualised peri-operative care.

Research

Future studies should thoroughly report known factors associated with chronic pain, whether patient, surgical, anaesthetic or analgesic. The long-term physical, psychological and functional outcomes should be detailed. Patient blood samples should be stored for genetic analyses: large data sets may identify genes that make patients susceptible or resistant to persistent postoperative pain. A better understanding of the natural history and consequences of chronic postoperative pain would facilitate effective strategies for its prevention and treatment. Patients should be made aware of the risk of chronic postsurgical pain, particularly where there is a high risk due to the type of surgery or known patient risk factors. This will allow patients to make better informed decisions about whether to proceed with surgery and to understand that surgery may alleviate an existing, intermittent pain but in exchange for a different lifelong pain.

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