

Persistent postoperative pain: where are we now?

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Editor's key points

- The incidence and burden of persistent postoperative pain is a significant problem.
- Our understanding of the condition is hampered by the poor quality of much of the data.
- Psychosocial factors, preoperative pain, poorly controlled postoperative pain and nerve injury are often associated factors.
- As yet, there is no compelling evidence that the incidence of persistent postoperative pain can be influenced by specific interventions.

Summary. There has been considerable interest and controversy around persistent postoperative pain for several years. Most of the available data arise from studies with methodological problems (especially its definition in terms of duration, severity, and effect on quality of life and function); however, more recent investigations have begun to address these issues. Although the quoted incidence varies considerably, analysis of the most conservative data shows that there is no doubt that persistent postoperative pain is a significant clinical problem and a burden to those who suffer from it. There is a wealth of literature describing factors associated with increased likelihood of persistent postoperative pain. Although it is difficult to be precise, it is clear that psychosocial factors probably play a role in some situations and that significant preoperative pain, severe immediate postoperative pain, and nerve damage are often good predictors. There are some data indicating that the incidence and severity of persistent postoperative pain can be reduced by special perioperative interventions; however, as yet, the evidence is not compelling and consistent. A reliable prevention strategy is not yet emerging from the published literature and considerably more work is required to deliver this.

Keywords: nerve damage; persistent postoperative pain; postoperative pain syndromes; preoperative pain; psychosocial factors

Our attention was drawn to the problem of persistent postoperative pain by the pain research group in Dundee over 10 yr ago.^{1 2} Much has been published since then and this article summarizes many of the most influential papers and seeks to understand the current position.

How is persistent postoperative pain defined?

The lack of an accepted definition for persistent postoperative pain is a major barrier when interpreting the literature. This needs to be clear about time after surgery, severity of pain, and its effect on quality of life and function. No accepted definition is a major reason for the wide variation in the published incidence of persistent postoperative pain for any given procedure. Pain is often described as chronic if it persists 3 or 6 months after tissue healing and many have used these timeframes when investigating persistent postoperative pain. It has been suggested that persistent postoperative pain should be defined as pain persisting 2 months after surgery that cannot be explained by other causes; some have followed this definition.

It is accepted practice in the management of chronic pain to ascertain its effect on quality of life and function; persistent postoperative pain is of course chronic and any meaningful definition should involve these dimensions. Unfortunately, the majority of studies have not considered this, although

more recent investigators have included it in their study design. The need for a recognized and fit for purpose definition of persistent postoperative pain was highlighted in a recent review that considered the problems of past study design and how it should be improved in order to obtain more reliable and clinically significant data.³

What is the incidence of persistent postoperative pain?

Interpretation of the early work is bedevilled by the factors described above and poor study design. However, more recent data from studies of better design have become available. Table 1 gives a sample of reported incidences of persistent postoperative pain after a variety of surgical procedures from such studies. However, estimates vary widely; for example, mastectomy 20–50%, amputation 50–85%, hysterectomy 5–30%, cardiac surgery 30–55%, hernia repair 5–35%, and thoracotomy 5–65%.

It is likely that there are numerous factors affecting the incidence of persistent postoperative pain and we are aware of some of them. Therefore, we are not likely to obtain consistent estimates of its incidence, even with better designed studies. However, there is no doubt that persistent postoperative pain is a significant problem worthy of our attention. Overall, an estimate based on data available up to 2006 showed that the incidence of chronic pain after

Table 1 Incidence of persistent postoperative pain after a variety of surgical procedures from studies of reasonably good design

Surgery	Incidence (%)	Reference
Inguinal hernia	12	Aasvang and colleagues ⁸
CABG	44	Bar-El and colleagues ³⁵
Thoracotomy	52	Pluijms and colleagues ²⁷
Femoral popliteal bypass	23	Greiner and colleagues ³⁶
Pelvic trauma	48	Meyhoff and colleagues ³⁷
Hip arthroplasty	28	Nikolajsen and colleagues ³⁸
Gastrointestinal	18	Bruce and colleagues ³⁹
Amputation	27–30	Hanley and colleagues ⁶
Mastectomy	48	Poleshuck and colleagues ²²

Table 2 Factors often associated with increased likelihood of persistent postoperative pain

Severity of preoperative pain
Nerve injury
Psychosocial factors
Severity of immediate postoperative pain
Specific surgical interventions, e.g. mastectomy, thoracotomy, amputation
Extent of surgery

common surgery was 10–50% and that this was severe in 2–10%.⁴ Given the large number of surgical procedures performed each year, the burden on patients and society is likely to be very large indeed. For example, Macrea estimated that, even when using the lowest quoted figures, there are likely to be ~41 000 new cases each year in the UK alone.⁵

Can persistent postoperative pain be predicted?

A potential strategy for the prevention of persistent postoperative pain is to identify factors that may predict an increased likelihood. If we could do this, we may be able to target specific interventions to the most vulnerable patients or use the information when considering the need for surgery, its extent, or both. Various factors have been reported to be associated with the development of persistent pain after surgery. They probably vary with surgical procedure but Table 2 summarizes those most often quoted.

Preoperative pain

The severity of preoperative pain has been shown in many studies to correlate with the development of persistent

postoperative pain. This was first appreciated in patients with phantom limb pain after amputation.^{6–7} However, strong associations have been reported with other common procedures such as hernia repair⁸ and thoracotomy.⁹

Nerve injury

Lesions to peripheral nerves are often associated with persistent postoperative pain. This was the most important factor for post-thoracotomy pain in some studies,¹⁰ and evidence of nerve damage has been shown to be a significant predictor after hernia repair.⁸ Nerve damage is often associated with classical symptoms and signs of neuropathic pain, including those occurring spontaneously (e.g. burning, lancinating pain, dysaesthesia, paraesthesia) and those that can be evoked (e.g. allodynia, hyperalgesia, hyperpathia). Several mechanisms for pain after nerve damage are postulated,¹¹ including ectopic activity in the injured and neighbouring uninjured peripheral nociceptive afferents; increased expression of sodium channels; mal-regulation of receptor proteins (e.g. transient receptor potential V1, $\alpha_2\delta$ subunit of voltage-gated calcium channel);¹² and central sensitization (e.g. pro-inflammatory cytokine release, loss of GABAergic interneurons, coupling between adrenergic sympathetic and nociceptive afferent fibres).

Persistent inflammatory process

Surgical trauma results in the release of various inflammatory mediators (e.g. prostaglandins, cytokines) and these can sensitize sensory afferents and cause pain. Usually, this process subsides over time as the wound heals. In some cases, it is postulated that inflammatory process may persist (e.g. persistent inflammation around a mesh repair),¹³ resulting in plastic changes in the spinal cord. This mechanism is not likely to be a causal factor in most patients with persistent postoperative pain.

Genetic susceptibility

A significant proportion of the variability in response to acute and chronic painful stimuli, including surgery, may be the result of genetic variability. Indeed, a genetic component has been found in specific types of migraine¹⁴ and some rare syndromes associated with insensitivity to pain are thought to be caused by abnormal genetic information responsible for the α -subunit of the voltage-gated sodium channel Na(v)1.7.¹⁵ Also, variations in response to endogenous and therapeutic opioids have been linked to variants of the μ -opioid and catecholamine-O-methyltransferase genes.¹⁵ However, a recent meta-analysis of studies investigating μ -opioid gene variants cast significant doubt on their influence.¹⁶ In an accompanying editorial, Mogil¹⁷ was pessimistic about the likelihood of genotyping becoming a useful tool in the clinical management of pain in the near future. Therefore, it seems unlikely that some form of genetic screening will soon be available to assist in the management and prevention of persistent postoperative pain.

Psychosocial factors

It is well recognized that psychosocial factors play a significant role in the genesis of chronic pain and the nature and severity of the disability associated with it. Indeed, psychological approaches (e.g. cognitive behavioural therapy) are used widely and effectively for the management of many types of chronic pain.¹⁸ Several studies have suggested that psychosocial factors play a significant role in some forms of persistent postoperative pain. Table 3 lists some of these.

The potential importance of psychosocial factors was identified several years ago, particularly with respect to the outcome of spinal surgery. For example, a literature review published in 2001 revealed that a poor response to spinal surgery was associated with preoperative pain sensitivity, depression, anger, anxiety, and poor pain coping strategies.¹⁹

Henrichs-Rocker and colleagues²⁰ performed a systematic review of the psychosocial factors related to persistent postoperative pain after various surgical procedures. They identified 36 studies of sufficient quality to allow meaningful analysis. Depression, ‘psychological vulnerability’ (definition varied between studies), and stress were considered to be likely correlates with persistent postoperative pain. Neuroticism, gender, and poor education were considered unlikely predictors, and in this study, there was insufficient evidence to make conclusions about anxiety, self-control, vitality, self perception, expectations, sense of control, and social support. An important finding of this analysis was the identification of many poor quality studies highlighting the need for more prospective, well designed, and sufficiently powered investigations.

Recently, investigators have begun to address this and the precise effects of psychosocial factors in specific types of surgery are starting to emerge. For example, in a robust prospective study of 464 patients undergoing open or laparoscopic hernia repair, only four significant independent risk factors were identified: preoperative pain related to impairment of activities; preoperative pain to tonic heat stimulation; 30 day postoperative pain score; and groin sensory dysfunction at 6 months. Clearly, some of these factors have psychological elements within them, but preoperative anxiety and depression *per se* were not independent predictors in this group.⁸ It is clear that psychosocial

factors play an important role in the genesis of persistent postoperative pain; however, more work is needed to elucidate their precise nature and influence and also how best to negate them.

Severity of early postoperative pain

The severity of early postoperative pain is likely to be important in many situations. However, the size of this effect may vary with procedure. For example, as previously described, pain at 30 days after operation was reported as a significant independent predictor after hernia repair⁸ in a well-designed study, but a recent systematic review of chronic pain after thoracotomy showed that the evidence for this was variable and plagued by poor study design.¹⁰

Specific persistent postoperative pain syndromes: can they be prevented?

Chronic pain can occur after most types of surgery, but there are some well-described syndromes that are relatively common. Much of the data concerning persistent postoperative pain arise from studies on these conditions, including some that have investigated potentially preventative interventions.

Breast surgery

Persistent pain after breast surgery can occur in the scar, chest wall, and arm; it can be nociceptive or neuropathic in nature. Only a small proportion is attributable to nerve injury and, occasionally, it can be associated with brachial plexus neuropathy (e.g. radiotherapy, tumour infiltration) cervical radiculopathy, carpal tunnel syndrome, and pericapsulitis of the shoulder joint.

An early retrospective review revealed that chronic pain after breast surgery was more likely in younger patients, but the disease in this group was more severe and invasive.²¹ A more recent, well-designed prospective study utilizing multiple logistic and linear regression on data from 95 women²² showed that youth was the only independent predictor of significant pain at 3 months (48%). However, extent of surgery, radiotherapy, and increased immediate postoperative pain were good predictors of severity in those who developed chronic pain. In this study, there was no relationship with emotional factors.

It is well established that local analgesic procedures improve immediate postoperative pain; however, can this translate into a reduced likelihood of persistent postoperative pain? Kairaluoma and colleagues²³ followed up on an initial study describing the effect of paravertebral block on immediate postoperative pain after mastectomy by assessing their patients 1 yr later. Both the incidence of chronic pain (43% vs 77%) and its intensity was less in those who had received perioperative paravertebral block with local anaesthetic. The effect of anticonvulsants and antidepressants on early postoperative pain has been assessed widely and most data show an improvement in analgesia, a reduction in opioid requirement, or both. A recent placebo-controlled, double-

Table 3 Psychosocial factors that have been linked with increased likelihood of developing persistent postoperative pain

Anxiety
Depression
Catastrophizing
Illness perception
Poor coping strategy
Low sense of control
Poor social support
Expectations

blind study in patients undergoing mastectomy investigated the effect of placebo, gabapentin, and venlafaxine given for 10 days (starting on the night before surgery) on the incidence of persistent postoperative pain.²⁴ There was a small but statistically significant difference in pain scores on movement in the venlafaxine group after 6 months (VAS 22, 21, and 12, respectively) and gabapentin significantly reduced the amount of burning pain experienced compared with placebo and venlafaxine. However, there was no difference in the incidence of pain that was described as troublesome (6%, 4%, and 2%, respectively). Unfortunately, the study was not powered for chronic pain and, compared with other studies, its incidence was small.

Some more evidence that it might be possible to prevent chronic pain after breast surgery has been provided by Fassoulaki and colleagues. They investigated a multi-modal perioperative analgesic technique (gabapentin, EMLA cream, and wound ropivacaine vs placebos in addition to standard analgesia) and demonstrated a significant reduction in chronic pain at 3 months.²⁵ However, despite a large reduction at 6 months (30% vs 57%), this was not statistically significant, possibly as the result of a type II error (only 41 patients in total had pain at 6 months). Using a similar model, the same team measured the effect of perioperative gabapentin, mexiletine, and placebo on the incidence of pain 3 months after breast surgery.²⁶ Again, the study was probably underpowered for this endpoint (66 patients in total), and there was no significant difference in the incidence of chronic pain (54%, 45%, 58%, respectively). However, there was a significant difference in the incidence of pain described as burning at 3 months (4%, 4%, 29%, respectively).

Thoracotomy

The incidence of chronic pain after thoracotomy also varies widely (25–60%),^{27–29} but it is a significant clinical problem. Pain may be related to the scar but can be experienced anywhere in the chest and back. A neuropathic component has been shown to be a feature in about 35–80% of cases,^{30–31} including allodynia, dysaesthesia, and burning. In a large study (225 patients), Pluijms and colleagues²⁷ found that chronic pain was associated with duration and severity of immediate postoperative pain and extent of surgery. There was no association with gender.

Unfortunately, there is little evidence to date to show that it might be possible to prevent this condition. Not many studies have been published and most are not well designed. A recent study investigated the effect of perioperative ketamine on 86 patients and found no reduction in chronic pain at 4 months.³² A comprehensive review of chronic post-thoracotomy pain by Wildgaard and colleagues¹⁰ concluded that although there was some suggestion that pre-emptive analgesic techniques may be helpful, there was no reliable evidence for a beneficial effect of any analgesic intervention.

Lower limb amputation

Phantom limb pain after amputation is the most recognized and well-described persistent post-surgical pain syndrome. There was considerable interest about 15 yr ago when some studies suggested that pre-emptive epidural analgesia may reduce the incidence of chronic phantom limb pain. However, later studies tended not to confirm this and those assessing other prevention techniques were also not convincing.⁷ A recent review analysed data from studies investigating post-amputation pain after surgery for peripheral vascular disease.³³ Eleven studies were identified involving pharmacological, epidural, and regional analgesia techniques. Only one of these studies (epidural infusion of diamorphine, clonidine, and bupivacaine) showed benefit; however, this was a small study with several methodological flaws.³⁴

Where are we now?

Despite the uncertainties surrounding the problem of persistent postoperative pain, we can be clear about a number of issues. First, persistent postoperative pain is a relatively common problem affecting thousands of patients in the UK and many more worldwide. These patients represent a significant proportion of the work in many chronic pain clinics and are often difficult to manage. The likelihood of persistent postoperative pain after some types of surgery should be a factor in the risk–benefit analysis before proceeding to surgery and should be discussed during the consenting process if data show that it is not uncommon.

Prevention is the key to the problem, but unfortunately we have made little progress in this area as yet. We have considered some evidence that this may be possible using approaches currently available and a few studies have shown benefit. However, the effect is often small and the evidence is not consistent. Presently, there is nothing to suggest that a reliable and effective technique for prevention is about to emerge.

The problem of poor study design has been highlighted many times in this article and by others. In order to make further progress, there is a clear need to ensure that present and future studies are designed appropriately. The ideal study design suggested by Kehlet and Rathmell³ was derived after consideration of the present evidence base and is highly recommended.

As far as clinical practice is concerned, perhaps the data do point to a way forward. The severity of postoperative pain has been recognized as a predicting factor for persistent pain in many studies. We do have excellent techniques to address this and it may be that concentrating more attention on patients who are in severe pain after surgery will be of benefit. Also, early specialist management of patients who are showing signs of developing persistent postoperative pain may also be beneficial. In many cases, this will require more intense postoperative follow-up aimed at detecting this specific problem. Most would agree that this is an approach based on common sense but, as yet, there are no reliable data to endorse it.

Conflict of interest

None declared.

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