

Chronic Post-surgical Pain

a report by

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Chronic pain after surgery (chronic post-surgical pain (CPSP)) is common but is often not recognised or may be neglected or misdiagnosed. Chronic pain is costly to society in terms of suffering and disability. For humanitarian, medical and economic reasons, the problem of chronic pain after surgery should be addressed.¹

In 1992, a survey of patients attending pain clinics in Scotland and the north of England demonstrated that 20% of these patients implicated surgery as one of the causes of their chronic pain and, in about half of these, it was the sole cause.²

Definition

In order for pain to be classified as CPSP, the following criteria need to be satisfied:

- the pain developed after a surgical procedure;
- the pain is of at least two months duration;
- other causes for the pain have been excluded (for example continuing malignancy or chronic infection); and
- the possibility that the pain is continuing from a pre-existing problem must be explored and exclusion attempted. (There is an obvious grey area here in that surgery may simply exacerbate a pre-existing condition, but attributing pain to the

surgery is clearly not possible as natural deterioration cannot be ruled out.)³

CPSP Syndromes

Limb Amputation

After limb amputation, pain syndromes fall into two broad categories: stump pain (sometimes called residual limb pain) and phantom pain. The prevalence of stump pain varies from 5% in a study of amputees attending a prosthetics factory⁴ to 62% in a study of US army veterans.⁵ The incidence of phantom limb pain is 30% to 81%.^{6,7} Using sophisticated scanning techniques, it has been demonstrated that the sensory cortex remaps after amputation. The loss of a limb or part of a limb also causes other problems for the central nervous system (CNS), which may involve the visual pathway and the motor control system. These changes may contribute to the development of phantom limb pain.³ Predictors of this pain include preamputation pain and persistent stump pain (acute and chronic). No conclusive study has evaluated the effect of acute or subacute stump pain control on long-term stump pain or long-term phantom limb pain.¹

Thoracotomy

Bertrand, et al. found that 53 of 87 patients and 92 of 146 patients developed chronic pain after posterolateral thoracotomy and video-assisted thoracic surgery, respectively.⁸ Its aetiology may

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5. R A Sherman, C J Sherman and L Parker, "Chronic phantom and stump pain among American veterans: results of a survey", *Pain*, 18 (1984), pp. 83–95.
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8. P C Bertrand, J F Regnard and L Spaggiari, et al., "Immediate and long-term results after surgical treatment of primary spontaneous pneumothorax by VATS", *Ann. Thorac. Surg.*, 61 (1996), pp. 1,641–5.

depend on nerve damage (more severe after chest wall resection)⁹ and intercostals nerve dysfunction (loss of superficial abdominal reflexes).¹⁰ Predictors for this syndrome (when tumour recurrence is excluded) include the severity of acute post-operative pain and intercostal nerve dysfunction (which may link more acute pain and persistent pain).⁹

Breast Surgery

Women who undergo breast surgery experience chest wall, breast or scar pain (range 11% to 57%), phantom breast pain (13% to 24%) and arm and shoulder pain (12% to 51%). The incidence of pain in one or more of these sites is close to 50% one year after breast surgery for cancer.¹ Much of the pain after breast surgery has been attributed to nerve damage (whether from surgery or radiation).¹¹

Predictive factors are the severity of acute post-operative pain, the presence of pain before surgery, the type of surgery, intercostobrachial nerve damage, adjuvant radiation therapy and possibly pre-operative anxiety or depression.¹

Cholecystectomy

Chronic abdominal pain after cholecystectomy is common (range 3% to 56%) but is less frequent than the pre-operative incidence of pain (83% to 100%).¹ Pathogenic factors include post-operative somatic incisional pain, sphincter of Oddi dysfunction, bile duct stones, ulcer, colonic dysfunction and scar pain.¹² Predictive factors include psychological vulnerability, long-standing pre-operative symptoms (including pain) and pain at six weeks after surgery.¹²

Inguinal Hernia Surgery

Chronic pain after inguinal hernia repair is less common than chronic pain after the surgeries cited previously. Because hernia surgery is common, a large number of individuals are affected by chronic pain.¹ The incidence of chronic pain after inguinal hernia repair varies from 0%¹³ to 37%¹⁴. In a prospective study of 500 procedures, surgery for recurrent hernia had a higher incidence of moderate-to-severe pain at 12 months than did surgery for a primary repair.¹⁵ The demonstrated relation between post-operative sensory dysfunction and chronic pain supports the interpretation that nerve damage is a pathologic factor.¹⁶ The extent of pain at one and four weeks after surgery is a predictive factor for pain at one year.¹⁵

Other Procedures

Chronic pain after orthopaedic surgery has been the subject of very few studies. A retrospective study of 500 patients after total hip replacement reported an incidence of pain on sitting of 16% and pain on walking of 35% at 102 (42–171) months.¹⁷

Following lumbar sympathectomy, a burning pain in the thigh may develop and typically lasts two to three months. Its incidence has been variously quoted as 12% to 35% after both open sympathectomy¹⁸ and percutaneous phenol injection¹⁹. In contrast to many other pain syndromes following surgical procedures, this syndrome is usually self-limiting.

Two distinct chronic pain syndromes have been reported after dental surgery: post-traumatic dysaesthesia (5% to 13%) and phantom tooth pain (3%).³

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11. T Tasmuth, K von Smitten and P Hietanen, et al., "Pain and other symptoms after different treatment modalities of breast cancer", *Ann. Oncol.*, 6 (1995), pp. 453–9.

12. T Jorgensen, J S Teglbjerg and P Wille-Jorgensen, et al., "Persisting pain after cholecystectomy: A prospective investigation", *Scand. J. Gastroenterol.*, 26 (1991), pp. 124–8.

13. I M Rutkow and A W Robbins, "The mesh plug technique for recurrent groin herniorrhaphy: A nine-year experience of 407 repairs", *Surgery*, 124 (1998), pp. 844–7.

14. The MRC Laparoscopic Groin Hernia Trial Group, "Laparoscopic versus open repair of groin hernia: A randomized comparison", *Lancet*, 86 (1999), pp. 1,528–31.

15. T Callesen, K Bech and H Kehlet, "Chronic pain after inguinal hernia repair - a prospective study after 500 operations", *Br. J. Surg.*, 86 (1999), pp. 1,528–31.

16. J F Gillion and P L Fagnicz, "Chronic pain and cutaneous sensory changes after inguinal hernia repair: Comparison between open and laparoscopic techniques", *Hernia*, 3 (1999), pp. 75–80.

17. R Johnson and K G Thorngren, "Function after total hip replacement for primary osteoarthritis", *Int. Orthop.*, 13 (1989), pp. 221–5.

18. N H Raskin, S A Levinson and P M Hoffman, et al., "Postsympathectomy neuralgia", *Am. J. Surg.*, 128 (1974), pp. 75–8.

19. W Reid, J Kennedy Watt and T G Gray, "Phenol injection of the sympathetic chain", *Br. J. Surg.*, 57 (1970), pp. 45–50.

In conclusion, a wide variety of operations have been shown to be associated with chronic pain syndromes and it is likely that, for the others, the problem also exists but has not been documented.

Mechanism

Currently, we have no understanding of the algogenic substances that are released to activate and sensitise the nociceptive nerve terminals in a surgical wound. Which classes of nociceptors are activated by these substances? How is this nociception integrated in the CNS as acute post-operative pain? The models describing the pathophysiology of sensory changes that occur after injury (largely developed from studies on inflammation in animals) may not translate well to post-operative pain in humans. For example, pain from incisions may be related to ischaemia, and inflammation may be less critical than originally proposed.²⁰

Similar to nerve injury, surgical tissue injury has been shown to result in spinal sensitisation, i.e. metabolic activation and hyperexcitability of spinal nociceptive neurons, expansion of sensory receptive fields and alterations in the processing of innocuous stimuli. These post-operative neuroplastic changes underlie the development of 'pathologic' pain, which is characterised by hyperalgesia (an increased response to a stimulus that is normally painful) that may be primary (at the site of injury) or secondary (distant to the site of injury), and allodynia (pain due to a stimulus that does not normally provoke pain).

Nitric oxide (NO) may play a role in both the development and maintenance of hyperalgesia.²¹ Three alternative mechanisms have been proposed to account for NO-induced nociceptor sensitisation:

- NO may enhance the release of an algogenic substance, i.e. prostaglandin E₂ (PGE₂);
- NO may inhibit the action of an endogenous antinociceptive substance that acts on peripheral nociceptors; or
- NO might act directly on the nociceptors.²²

Furthermore, pharmacologic studies indicate

that central sensitisation is at least partially mediated by activation of N-methyl-D-aspartate (NMDA) receptors, which could lead to ultimate NO production.

Perioperative Analgesia and CPSP

The most striking predictive post-operative factor is the severity of acute post-operative pain after breast surgery, thoracic surgery and hernia repair.

The link between early post-operative pain and chronic pain does not necessarily imply causality but is nonetheless interesting and deserves further investigation.

Kawamata, et al.²³ subjected volunteers to a small incision in the volar forearm and then mapped the area of hyperalgesia caused by incision. Secondary hyperalgesia (hyperalgesia outside of the injured area) is one measure of enhanced responsiveness of the CNS, i.e. central sensitisation. It was noted that the area of flare or redness (possibly a result of axon reflexes) caused by incision was distinct from the area of hyperalgesia. The large area of hyperalgesia did not develop when a local anaesthetic injection was given before the incision. De Kock, et al.²⁴ demonstrated that reducing the area of hyperalgesia after colectomy did not greatly reduce acute pain, but was associated with a decrease in the number of patients who developed residual pain as late as six months after colectomy. Therefore, the area of hyperalgesia – one measure of central sensitisation – could perhaps predict patients likely to develop persistent pain after surgery.

Several studies suggest that effective treatment of acute pain after surgery can reduce the incidence of CPSP. It seems that the specific modality of pain relief is not as important as the degree of analgesia achieved. Prospective randomised studies are needed to determine how different pain management strategies influence the incidence of CPSP.

Future Strategies

If persistent pain after surgery results from sensitisation, prevention may be possible if sensitisation can be blocked.

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Pre-emptive Analgesia

If the trigger signal is prevented from gaining access to the CNS, pain would be diminished, and treatment aimed at reducing any enhanced excitability within the CNS initiated by a trigger would reduce hyperalgesia and allodynia. Thus, the concept of pre-emptive analgesia for post-operative pain was developed. Two methods are available for preventing central sensitisation: conduction blockade with local anaesthetics and suppression of the excitability of the nervous system before it receives the nociceptive input. Many trials evaluating pre-emptive analgesia have been conducted in patients undergoing elective surgery, but the results have been inconclusive.²⁵

Multimodal Analgesia

Pre-emptive multimodal analgesia not only improves short-term recovery, but may theoretically prevent chronic post-surgical pain by preventing suprasensitisation of the CNS irrespective of the surgical injury. Pre-operative opiates and non-steroidal anti-inflammatory drugs (NSAIDs), preincisional regional block and post-operative continuous paravertebral block or epidural, together with NSAIDs, have been promoted as the ideal combination for near total analgesia following thoracotomy.¹⁰

Regional Anaesthesia/Analgesia

Obata, et al., in a prospective, randomised, single-blind study, demonstrated a significant effect of combined intraoperative and post-operative epidural analgesia when compared with post-operative epidural analgesia alone for posterolateral

thoracotomy (decreasing the incidence of pain at six months from 67% to 33%).²⁶

Timing of Surgery

Some early reports indicated that the incidence of phantom limb pain decreased with prolonged (72 hour) pre-operative epidural pain control, followed by post-operative epidural pain control.^{27,28} In a subsequent randomised controlled study, this observation was not confirmed. When pre-operative epidural pain control was limited to 18 hours, the extent and intensity of perioperative blockade was not sufficient to control pain without systemic opioids.⁷

Nitric Oxide

Recent animal research suggests that, in the periphery, NO modulates the response to a noxious stimulus. This effect may result either from the facilitation of cyclic adenosine monophosphate (cAMP) stimulation by hyperalgesic mediators or by direct stimulation of the cyclic guanosine monophosphate (cGMP) pathway. In animal models, NO donors inhibit inflammatory hyperalgesia, an effect that is blocked by guanylyl cyclase inhibitors. A new class of NO-releasing NSAIDs is being developed, releasing nitric oxide in relatively small amounts over a prolonged period of time (six to 12 hours).²⁹ Furthermore, plasma concentrations of stable NO products may be a useful predictor of subsequent development of CPSP.

CPSP is a common, important and under-recognised problem. It appears that the most effective approach to decreasing its incidence may be to optimise analgesia in the perioperative period. ■

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