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Pain after thoracotomy

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Key points

- Poorly managed thoracotomy pain can result in postoperative pulmonary complications.
- The multifactorial pathophysiology of thoracotomy pain mandates a multimodal approach to analgesia.
- Paravertebral infusion provides similar analgesia to thoracic epidurals with less respiratory complications and hypotension.
- Chronic pain after thoracotomy can affect more than 50% of patients.

Thoracotomy is considered the most painful of surgical procedures and providing effective analgesia is the onus for all anaesthetists. Ineffective pain relief impedes deep breathing, coughing, and remobilization culminating in atelectasis and pneumonia. This article reviews the mechanisms of acute and chronic thoracotomy pain, the risk factors, current analgesic options, and the role genetics may increasingly play in the management of thoracotomy pain.

Pathophysiology of thoracotomy pain

Pain after thoracotomy arises from *nociceptive* and *neuropathic* mechanisms which may originate from somatic and visceral afferents. Pain can also be *referred*.

Nociceptive somatic afferents are conveyed by the intercostal nerves after skin incision, rib retraction, muscle splitting, injury to the parietal pleura, and chest drain insertion to the ipsilateral dorsal horn of the spinal cord (T4–T10). The afferents are then transmitted to the limbic system and somatosensory cortices via the contralateral anterolateral system of the spinal cord. *Nociceptive visceral* afferents are conveyed by the phrenic and vagus nerves after injury to the bronchi, visceral pleura, and pericardium.

In response to this tissue injury, inflammatory mediators, such as prostaglandins, histamine, bradykinin, and potassium, are released. These mediators directly activate nociceptors, enhance their activity, and reduce the pain threshold. This amplified response to pain is called primary sensitization and leads to intensified pain on breathing or coughing after operation.

Continued nociception during the perioperative period leads to hyperexcitability of the dorsal horn neurones and higher pain centres through activation of *N*-methyl-D-aspartate (NMDA) receptors in response to substance P, calcitonin gene-related peptide, and glutamate, which causes central sensitization. This, along with the development of neuropathic pain, can herald the onset of chronic pain which is defined as pain that persists or recurs along the site of the thoracotomy incision at least 2 months after the procedure.

Neuropathic pain, after intercostal nerve injury, develops via the mechanisms shown in Figure 1, and results in the paradox of reduced sensory input (from touch, temperature, and pressure) with hypersensitivity (dysaesthesia, allodynia, hyperalgesia, and hyperpathia).[1]

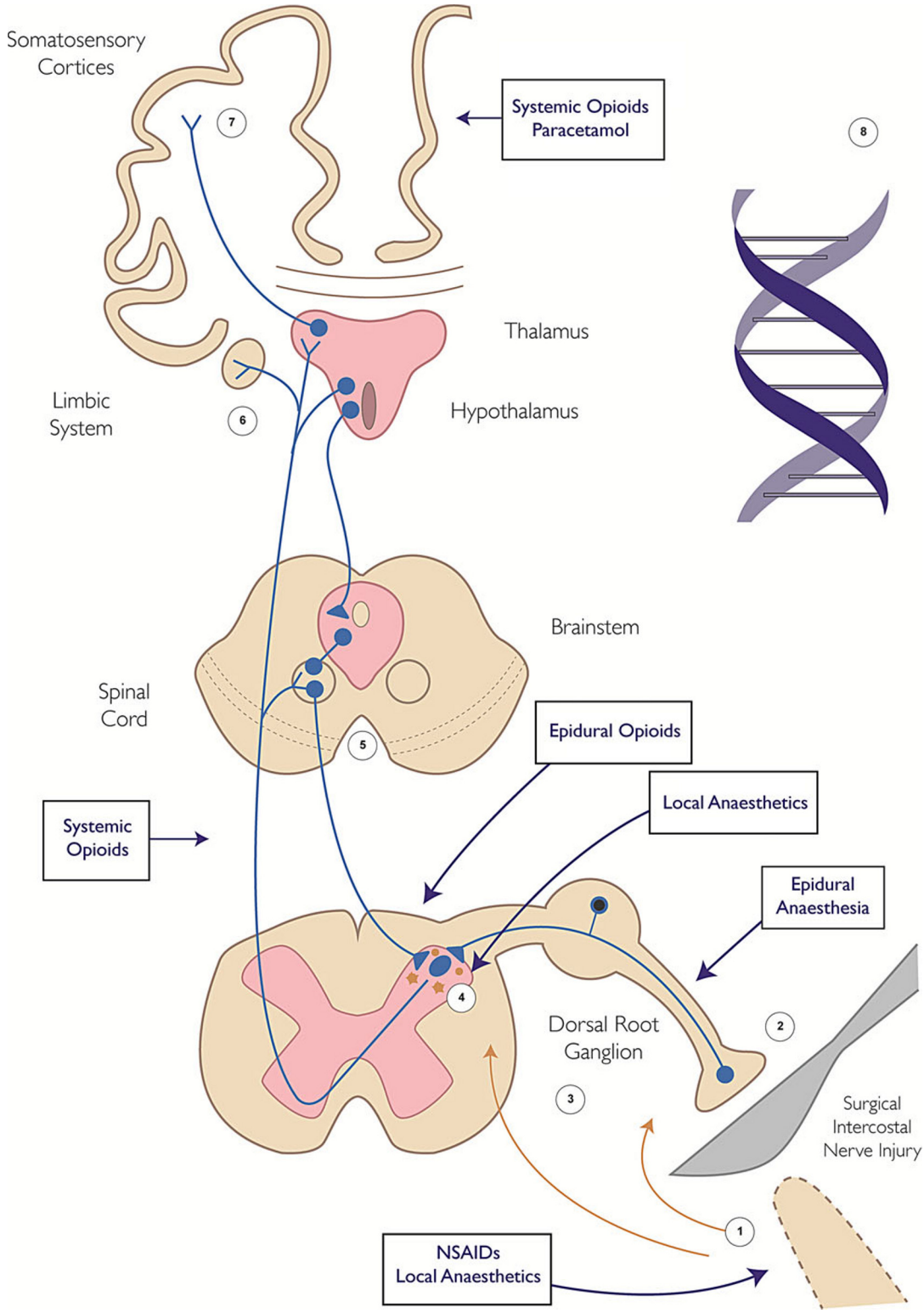

Fig 1 Pain pathway showing mechanisms of neuropathic pain and sites of analgesic action. (1) Denervated Schwann cells and infiltrating macrophages distal to nerve injury produce local and systemic mediators that drive pain signalling. (2) Neuroma at the site of injury is a source of ectopic spontaneous excitability in sensory fibres. (3) Changes in gene expression in dorsal root ganglion alter excitability, responsiveness, transmission, and survival of sensory neurones. (4) Dorsal horn is the site of altered activity and gene expression, producing central sensitization, loss of inhibitory interneurons, and microglial activation, which together amplify sensory flow. (5) Brainstem descending controls modulate transmission in the spinal cord. (6) The limbic system and hypothalamus contribute to altered mood, behaviour, and autonomic reflexes. (7) Sensation of pain generated in the cortex (past experiences, cultural inputs, and expectations converge to determine what patient feels). (8) Genomic DNA predispose (or not) the patient to chronic pain and affect their reaction to treatment. Reprinted from Kehlet and colleagues,[1] © 2006, with permission from Elsevier.

Referred pain to the ipsilateral shoulder is common after thoracotomy and can often be unresponsive to the effects of thoracic epidural analgesia (TEA). Studies have demonstrated a reduction in shoulder pain by infiltrating local anaesthetic to block the phrenic nerve at the level of the pericardial fat pad, or alternatively by interscalene block. This suggests that irritation of the visceral pleura and pericardium, referred to the shoulder by the phrenic nerve, is the most likely source of this pain. As the nerves arise from C3 to C5, TEA is ineffective in blocking this pain. The phrenic nerve may also convey referred pain from transection of a major bronchus or irritation of the pleura from a chest drain placed too far into the apex of the hemithorax.[2]

Factors affecting thoracotomy pain

Surgical factors

The posterolateral approach to thoracotomy provides the best surgical access. However, it involves dividing the latissimus dorsi, and at times the serratus anterior and trapezius muscles, resulting in one of the most painful surgical incisions. Many surgeons now use alternative muscle-sparing approaches where incision of the muscles is replaced with dissection and reflection onto the ribs. The reduced field of view, however, may lead to excessive rib retraction, fracture, dislocation, costovertebral disruption, and damage to the intercostal nerves. These incisions may also span multiple dermatomes as opposed to the single dermatome of the posterolateral approach; for example, the axillary incision extends vertically downwards. Alternatively, an increasing number of video-assisted thoracoscopic surgery (VATS) is performed which may reduce acute pain if intercostal nerve damage is avoided by limiting the number and size of intercostal ports used. However, the incidence of chronic pain appears to be similar to open thoracotomy.[3]

Patient factors

Although studies from the general surgical population suggest that patients who are young, of female gender, with a history of depression and anxiety and who are poorly informed about their management plan are more likely to experience acute post-surgical pain,[4] these risks have not been demonstrated in thoracotomy patients.

Treatment of post-thoracotomy pain

The multifactorial nature of acute thoracotomy pain precludes the use of any single analgesic technique to block all the pain afferents described above. Success is more likely with a multimodal approach that targets multiple sites along the pain pathway (Fig. 1), and incorporates regional anaesthesia with non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and other parenteral adjuncts.

Regional anaesthesia

Thoracic epidural analgesia

TEA is a widely used analgesic technique for thoracotomy.[5] Insertion of a thoracic epidural *before* general anaesthesia facilitates patient feedback on improper placement and permits the assessment of its efficacy. The insertion point is usually midway along the dermatomal distribution of the thoracotomy incision at the level of T5–T6. Difficulty in locating the epidural space is often encountered due to the steep caudal angulation of the spinous processes at this level; therefore, some anaesthetists prefer a paramedian approach which avoids the spinous processes (Fig. 2).

A combined local anaesthetic/opioid epidural solution is most commonly used. Local anaesthetics synergistically increase bioavailability of opioids in the cerebrospinal fluid (CSF), increase their binding to μ-receptors, and block the release of substance P in the substantia gelatinosa of the dorsal horn of the spinal cord. The choice of opioid depends on its lipophilicity, which influences its rate of systemic absorption. A sample regimen involves a test dose of 3 ml 0.5% l-bupivacaine followed by 0.1 ml kg^{-1} of 0.25% l-bupivacaine to establish the block. An infusion can then be commenced of 0.1–0.125% l-bupivacaine + 2–5 μg ml^{-1} fentanyl at 0.1 ml kg^{-1} h^{-1}. The dose can be reduced in the elderly who exhibit increased epidural spread.

Paravertebral analgesia

The paravertebral space is a potential space lateral to the vertebral column that lies posterior to the parietal pleura and anterior to the costotransverse ligament through which the spinal nerves (including their anterior and posterior rami and white and grey rami communicantes) pass *en route* from the intervertebral

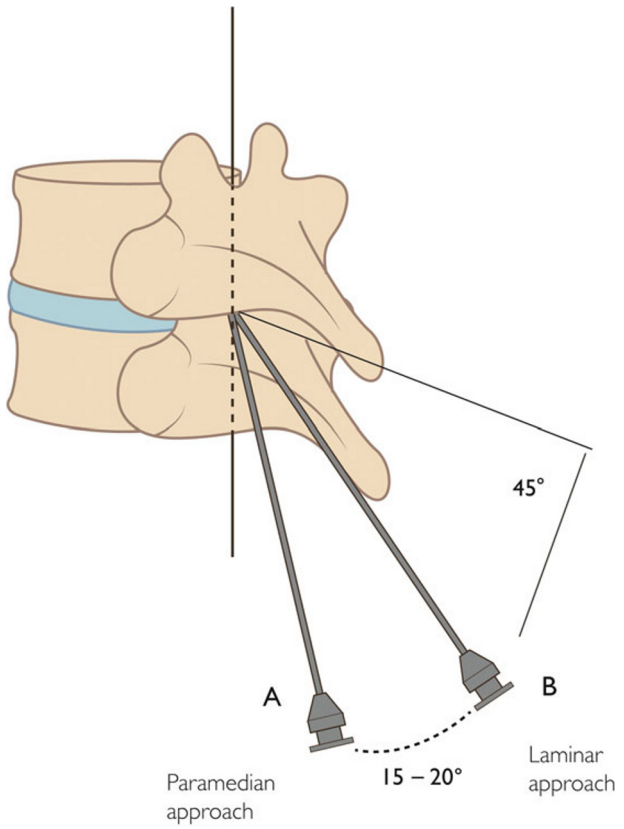

Fig 2 Insertion of paramedian thoracic epidural. The needle is inserted 1 cm lateral to the superior tip of the spinous process and then advanced perpendicular to all planes to contact the lamina of the vertebral body immediately below. The needle is 'walked' up the lamina at an angle rostrally (45°) and medially (20°) until the rostral edge of the lamina is felt. The needle is advanced over the edge of the lamina, seeking a loss of resistance on entering the epidural space after transversing the ligamentum flavum. The laminar approach (B) is favoured by other practitioners. The needle is inserted next to the rostral edge of the spinous process and advanced straight without any angle from the midline. Diagram adapted with permission from Anaesthesia for thoracic surgery, Slinger, PD, Campos, JD. In: *Miller's Anesthesia*, 7th Edn, Miller, RD, and colleagues, eds, 1819–88, © Elsevier 2009.

foramen to the intercostal space (Fig. 3). The lack of a surrounding fascial sheath facilitates *unilateral* nerve block using either a percutaneous loss of resistance technique or preferably an open technique where the surgeon incises and dissects the parietal pleura overlying the paravertebral gutter, threads a catheter, and sutures the pleura closed (Fig. 3). Alternatively, it can be done percutaneously under thoracoscopic or ultrasound guidance.

Although comparable with TEA, paravertebral analgesia (PVA) is less familiar and may fail due to misplacement of the catheter, inadequate dermatomal spread, or failure to maintain local

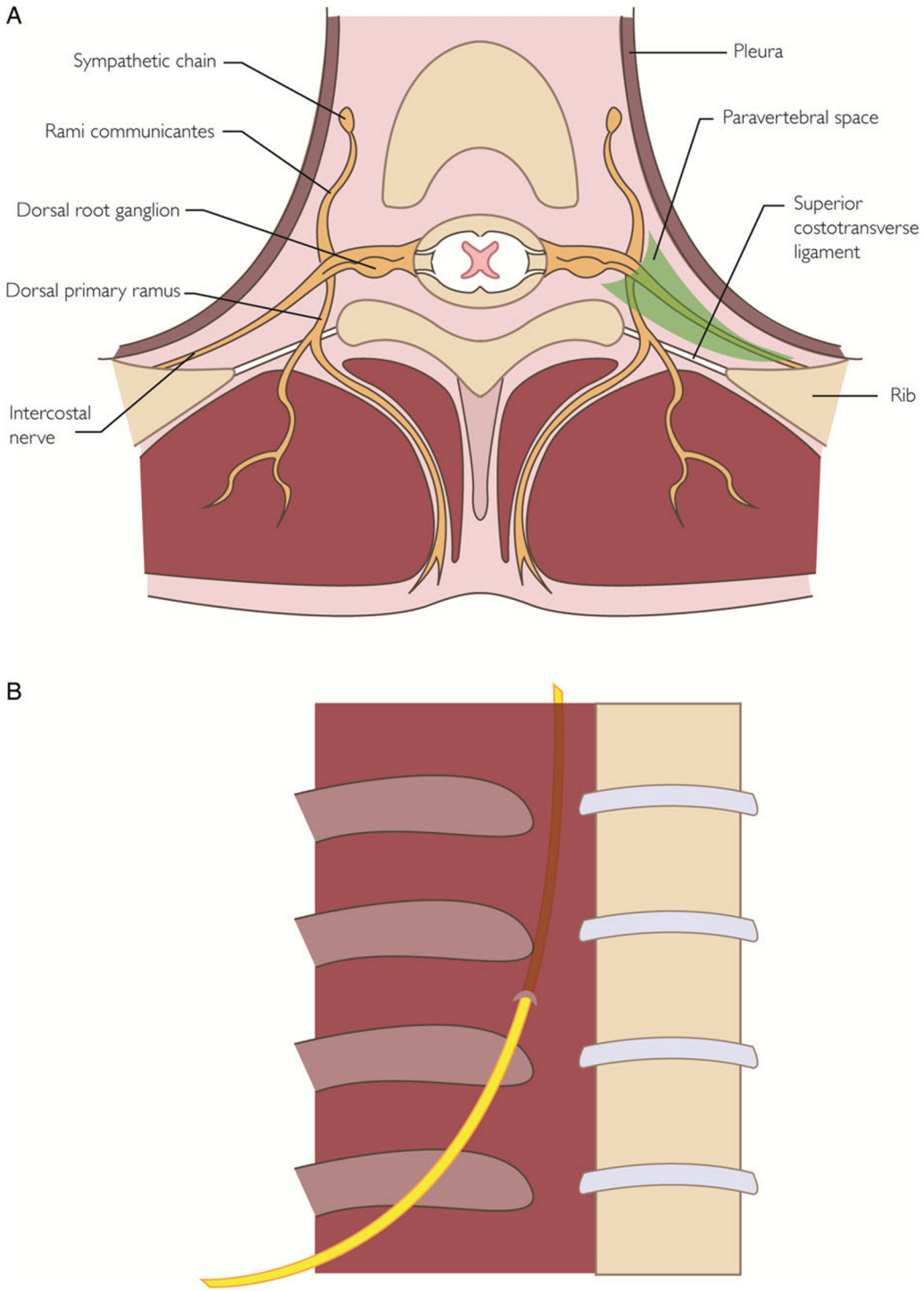

Fig 3 (A) The paravertebral space. (B) Open direct-vision placement of a paravertebral catheter intraoperatively. The epidural catheter is passed into the paravertebral space through a small defect created in the extrapleural (endothoracic) fascia. The proximal end of the catheter is then brought out of the chest through a separate needle puncture in an intercostal space near the chest drains. Diagram adapted with permission from Anaesthesia for thoracic surgery, Slinger, PD, Campos, JD. In: *Miller's Anesthesia*, 7th Edn, Miller, RD, and colleagues., eds, 1819–88, © Elsevier 2009.

anaesthetic within the paravertebral space if the pleura is not intact. The paravertebral space also lacks opioid receptors; therefore, local anaesthetic infusions may require supplementation with i.v. opioids. A sample regimen involves percutaneously placing 10 ml 0.25% l-bupivacaine at T3, T5, and T7 before skin incision, followed by an infusion of 0.125% bupivacaine at 0.2 mg kg^{-1} h^{-1} through a catheter placed by the surgeon under direct vision.

Intrathecal opioids

Intrathecal preservative-free opioids produce analgesia with doses much smaller than the epidural and i.v. routes via a multicompartmental mechanism.[6] On injection, opioids simultaneously spread cephalad within the CSF, bind to non-specific sites within white matter of the spinal cord and to opioid receptors in the dorsal horn, traverse the dura to enter the epidural space where they bind to epidural fat and enter the systemic circulation through vascular uptake. The speed of onset, duration of action, and degree of rostral spread depend on the effects of the lipophilicity of the opioid in each of these compartments. Morphine, a hydrophilic opioid, is commonly used in thoracotomy. It traverses the dura slowly, binds little to epidural fat, and entry to the systemic circulation is delayed. Morphine thus remains in relatively large concentrations in the CSF resulting in an onset of action within 1–2 h of administration and lasting up to 24 h. The technique can be combined with a paravertebral local anaesthetic infusion as an alternative to TEA. Patients must be observed for delayed respiratory depression, urinary retention, and must have an analgesic plan that extends beyond the duration of action.

Other regional techniques

When neuraxial analgesia is not feasible, intercostal nerve block coupled with systemic parenteral analgesia remains an option. The block is simple to perform either percutaneously or under direct vision intraoperatively. However, its limited duration of action (~6 h) necessitates repeating the block at multiple levels or starting an infusion. This increases the risk of systemic toxicity from the highly vascular intercostal space. Incomplete analgesia is also a problem since the dorsal rami supplying the back are not blocked, which is relevant in posterolateral thoracotomies, and the lateral cutaneous branch may also be missed if the block is performed too anteriorly.

Intrapleural analgesia, where local anaesthetics are injected between the layers of the parietal and visceral pleura, is not recommended. Surgery increases the volume of the interpleural space with blood and air which dilutes the spread of local anaesthetics. Systemic absorption of local anaesthetics is also considerable.

Systemic analgesia

Opioids

Epidural analgesia has been shown to be superior to i.v. morphine via patient-controlled analgesia (PCA) devices. Furthermore, the doses of opioids required to produce comparable analgesia when used as sole agents also produce significant respiratory depression; therefore, opioids are mainly relegated to adjuncts to a regional technique.

Non-steroidal anti-inflammatory drugs

The role of NSAIDs in thoracotomy is two-fold, to reduce opioid requirements and to treat ipsilateral shoulder pain resistant to TEA. NSAIDs reduce the inflammatory response to surgery by inhibiting the cyclooxygenase enzyme (COX) and consequently prostaglandin synthesis.[7] However, they should be used with care in the elderly who are especially vulnerable to renal dysfunction. NSAIDs may also reduce the effectiveness of pleurodesis procedures. Paracetamol shares the opioid-sparing and shoulder pain roles of NSAIDs with less side-effects.[7] Its analgesic effect with NSAIDs is additive.

Management of chronic post-thoracotomy pain

Chronic pain after thoracotomy afflicts up to 57% of patients at 3 months and 47% at 6 months.[8] This incidence has not improved since the 1990s despite improvements in perioperative care.[8] Patients present to the pain clinic describing a burning, numbness, or a cutting sensation along the thoracotomy scar, which may be constant or intermittent, and may be evoked by non-painful stimuli such as changes in temperature or donning clothing.

Perioperatively, the management of chronic post-thoracotomy pain (CPTP) should ideally begin with a review of any modifiable risk factors. A number of small studies have shown a reduction in chronic pain after TEA.[9] However, the concept of pre-emptive analgesia, where analgesics are administered before the noxious stimulus to prevent the peripheral and central sensitization implicated in chronic pain, has thus far little evidence to support it in the context of CPTP.[9]

Once a patient has developed CPTP, it is important to exclude other differential diagnoses such as malignancy recurrence or the effects of radiotherapy and chemotherapy. A multidisciplinary personalized plan incorporating behavioural therapies, pharmacological agents, and nerve blocks should then be devised. Agents used include NSAIDs, amitriptyline, gabapentin, opioids, and ketamine. The underlying goal of all these agents is to reduce the peripheral and central sensitization that has occurred. Non-pharmacological treatments used have shown varying success and include transcutaneous electrical nerve stimulation, cryoanalgesia, radiofrequency ablation, and spinal cord stimulation.

Epidural, paravertebral, or intrathecal morphine?

In a systematic review by the Procedure Specific Postoperative Pain Management working group (PROSPECT), paravertebral and thoracic epidural continuous infusions of opioid-free local anaesthetic were found to be comparable, but PVA was associated with less respiratory complications and hypotension.[10] Furthermore, in a Cochrane Review by the authors, PVB was found to be associated with lower rate of major complications including chest infection and acute confusion and minor complications such as low blood pressure, nausea and vomiting, itching and urinary retention when compared to TEA.[11] A single bolus of intrathecal opioid before operation was also comparable with both techniques. However, the duration of analgesia was limited to 24 h.[10]

Based on the review, PROSPECT recommend that either TEA with local anaesthetics and an opioid or continuous PVA with local anaesthetics combined with parenteral paracetamol and an NSAID should be used as first-line analgesia for thoracotomy. Where these techniques are not possible, or are contraindicated, intrathecal opioid or intercostal nerve block are recommended, which requires the use of supplementary systemic analgesia. The PROSPECT recommendations are summarized in Figure 4.

Although VATS is associated with less acute pain than open thoracotomy, it may still be significant if intercostal nerves are compressed by twisting instruments and the need for an incision to extract lobes. If the patient has poor respiratory reserve or their disease increases the likelihood of conversion to thoracotomy, TEA is advisable. Otherwise, the combination of PVA with i.v. PCA is a suitable alternative.[12]

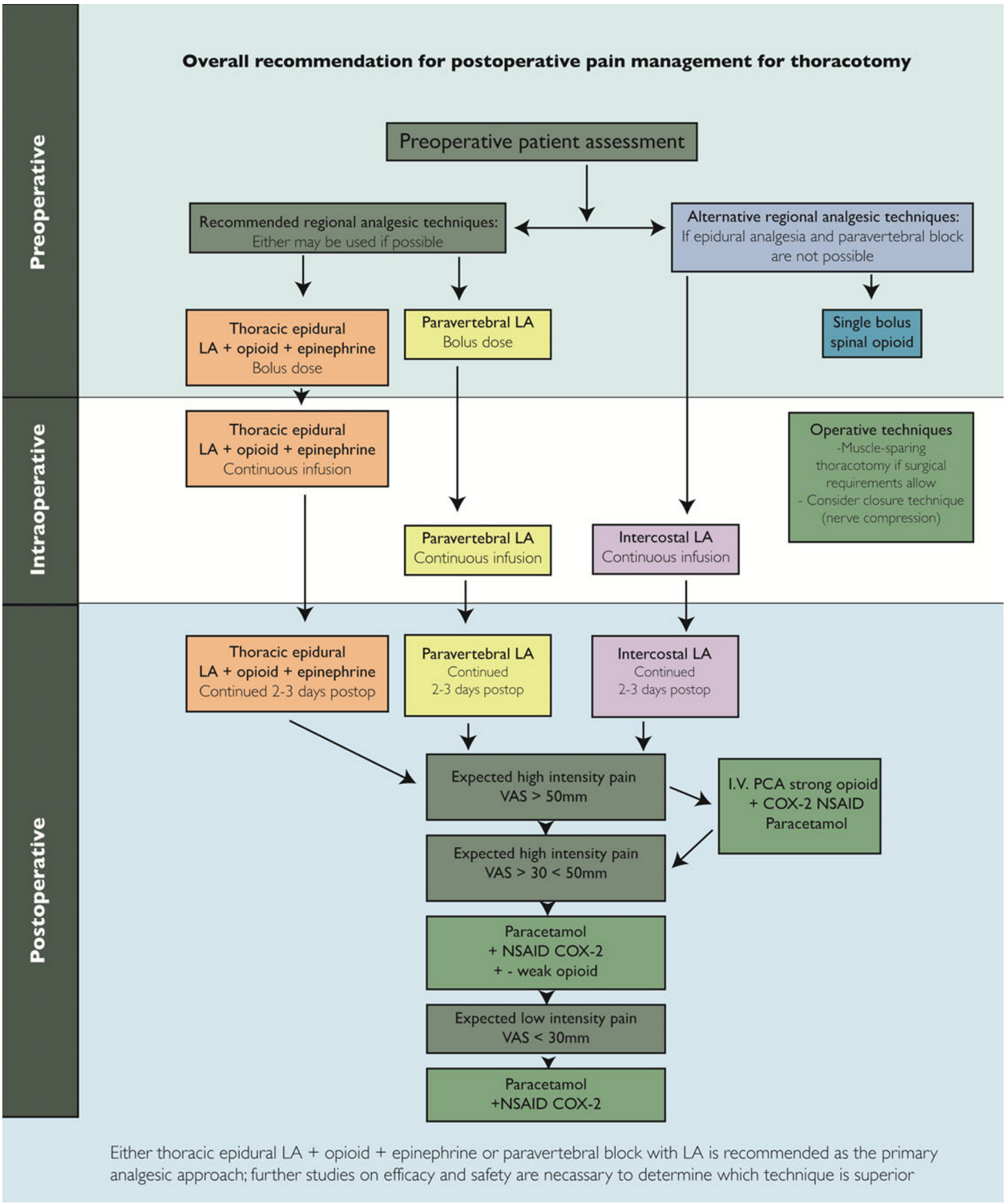

Fig 4 Algorithm proposed by the PROSPECT Working Group for pain management after thoracotomy. COX-2, cyclooxygenase 2; LA, local anaesthetic; VAS, visual analogue scale.

Genetics and thoracotomy pain

A patient's genes can change how he or she experiences thoracotomy pain. In addition to the effect on analgesic pharmacokinetics, genetic polymorphisms can have a profound influence on the sensation of thoracotomy pain such that the patient may be especially sensitive or conversely insensate to pain. For example, a mutation in the gene SCN9A, which encodes a sodium channel (NaV1.7), causes either a gain of function resulting in erythermalgia or loss of function resulting in the inability to sense pain.[13]

In addition to the purely genetic causes of altered nociception, epigenetic modifications may also play a role in CPTP. Epigenetics

is the way in which the environment changes gene expression through altering the chemical or physical structure of DNA. For example, the surgical injury may trigger a cascade of events that alter the structure of DNA by either methylation or histone modification which culminates in a change in gene expression leading to increased postoperative pain.

Preclinical studies have shown a reduction in the hypersensitivity that accompanies nerve injury by using histone deacetylase inhibitors to prevent histone deacetylation. This is particularly significant for surgery where there is a high risk of nerve damage such as thoracotomy. Other laboratory studies inhibiting DNA methyltransferase in an inflammatory pain model showed a reduction in hypersensitivity and reduced methylation in the prefrontal cortex and amygdala, which modulate feelings of depression, anxiety, and chronic pain.[14] These epigenetic processes therefore represent a target for future analgesic development.

Conclusion

The management of pain after thoracotomy requires a multimodal approach incorporating regional and systemic analgesia. The selection of an analgesic option should always be a balance between the risks and benefits of an individual technique and is a decision which should be tailored to the patient's comorbidities and wishes, the extent of surgery, and the local facilities available.

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Declaration of interest

None declared.

MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at https://access.oxfordjournals.org by subscribers to *BJA Education*.

References

1. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet* 2006; **367**: 1618–25
2. MacDougall P. Postthoracotomy shoulder pain: diagnosis and management. *Curr Opin Anaesthesiol* 2008; **21**: 12–5
3. Searle RD, Simpson MP, Simpson KH, Milton R, Bennett MI. Can chronic neuropathic pain following thoracic surgery be predicted during the postoperative period? *Interact Cardiovasc Thorac Surg* 2009; **9**: 999–1002
4. Ip HYV, Abrishami A, Peng PWH, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption. *Anesthesiology* 2009; **111**: 657–77
5. Shelley B, Macfie A, Kinsella J. Anesthesia for thoracic surgery: a survey of UK practice. *J Cardiothorac Vasc Anesth* 2011; **25**: 1014–7
6. Rathmell JP, Lair TR, Nauman B. The role of intrathecal drugs in the treatment of acute pain. *Anesth Analg* 2005; **101**: S30–43
7. Maxwell C, Nicoara A. New developments in the treatment of acute pain after thoracic surgery. *Curr Opin Anaesthesiol* 2014; **27**: 6–11
8. Bayman EO, Brennan TJ. Incidence and severity of chronic pain at 3 and 6 months after thoracotomy: meta-analysis. *J Pain* 2014; **15**: 887–97
9. Wildgaard K, Ravn J, Kehlet H. Chronic post-thoracotomy pain: a critical review of pathogenic mechanisms and strategies for prevention. *Eur J Cardiothorac Surg* 2009; **36**: 170–80
10. Joshi GP, Bonnet F, Shah R *et al*. A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. *Anesth Analg* 2008; **107**: 1040
11. Yeung JHY, Gates S, Naidu BV, Wilson MJA, Gao Smith F. Paravertebral block versus thoracic epidural forpatientsundergoing thoracotomy. *Cochrane Database Syst Rev* 2015, in press
12. Bottiger BA, Esper SA, Stafford-Smith M. Pain management strategies for thoracotomy and thoracic pain syndromes. *Semin Cardiothorac Vasc Anesth* 2014; **18**: 45–56
13. Cox JJ, Reimann F, Nicholas AK *et al*. An SCN9A channelopathy causes congenital inability to experience pain. *Nature* 2006; **444**: 894–8
14. Mauck M, Van de Ven T, Shaw AD. Epigenetics of chronic pain after thoracic surgery. *Curr Opin Anaesthesiol* 2014; **27**: 1–5