46
Pain Management After Thoracic Surgery

Stephen H. Pennefather and James McKevith

Key Points

- Thoracic surgery can cause significant pain and suffering. Appropriate analgesia is important both for humanitarian reasons and to allow early mobilisation and pulmonary rehabilitation. Poor pain relief can increase pulmonary complications and mortality.
- Pain after thoracic surgery is generated from multiple structures and is transmitted via a number of afferent pathways. Factors that affect pain post-operatively can be divided into patient factors, analgesic technique and surgical approach.
- Paravertebral catheters and thoracic epidural analgesia are widely used for thoracotomies and both have advantages and disadvantages. The optimal solutions for thoracic epidurals contain a low dose local anaesthetics combined with a lipophylic opioid. Paravertebrals with higher doses of local anaesthetic are more efficacious. Further direct comparisons between the two techniques are required to establish the role of each option.
- Opioid tolerant patients pose a particular challenge. Maintenance opioid should be continued peri-operatively to avoid withdrawal symptoms. A regional technique, supplemented with non-opioid analgesics is advised.

Introduction

A posterolateral thoracotomy is amongst the most painful incisions and thus unsurprisingly patients can, and sometimes do, suffer considerable pain in the post-operative period if analgesia is not managed appropriately. Poorly treated post-thoracotomy pain greatly reduces patient satisfaction, their quality of life and sometimes the quality of life of their loved ones. Under-treated pain can also reduce the patient's ability to co-operate with post-operative physiotherapy and remobilisation. The effectiveness of post-thoracotomy pain control can perhaps best be determined by assessing the patient's ability to participate in post-operative physiotherapy and other rehabilitation regimens. Effective pain control can facilitate a reduction in post-operative complications, particularly post-operative pulmonary complications. Over the years a large number of drugs, combinations of drugs and techniques to deliver these drugs have been developed and used to control post-thoracotomy pain. Unfortunately, no technique has emerged that is safe, effective and applicable to all patients. Until the early 1980s, systemic opioids formed the mainstay of post-thoracotomy analgesia in the West. Thoracic epidurals were introduced into clinical practice for post-thoracotomy

P. Slinger (ed.), *Principles and Practice of Anesthesia for Thoracic Surgery*,
DOI 10.1007/978-1-4419-0184-2_46, © Springer Science+Business Media, LLC 2011

analgesia in the mid-1970s [1, 2] and had become the gold standard of post-thoracotomy analgesia by the mid-1990s [3]. Somatic paravertebral blocks are now gaining acceptance as an alternative method for providing post-thoracotomy analgesia. A number of factors have led to the increased use of somatic paravertebral blocks. The risks associated with the peri-operative use of epidural analgesia are becoming clearer and are perhaps greater than previously thought [4, 5]. More patients are presenting for thoracic surgery on multiple antiplatelet agents sometimes with intra-coronary stents in situ. While dual antiplatelet therapy is known to be a contraindication to thoracic epidural analgesia [6] the risk of discontinuing antiplatelet agents peri-operatively is now quantifiable [7–9]. Few randomised studies have compared outcomes after thoracic epidural analgesia or paravertebral block. The limited results available, however, suggest that paravertebral blocks may be are more effective at reducing respiratory complications then thoracic epidural analgesia and after the first few hours provide equivalent analgesia [10, 11] (see Figs. 46.1 and 46.2).

Well-informed patients may experience less pain [12] so whenever possible patients should receive a full explanation of the proposed analgesic technique and its likely effects including its limitations, potential side effects and incidence of complications. The relative merits of the alternative strategies should also be discussed. How much to tell patients about potential

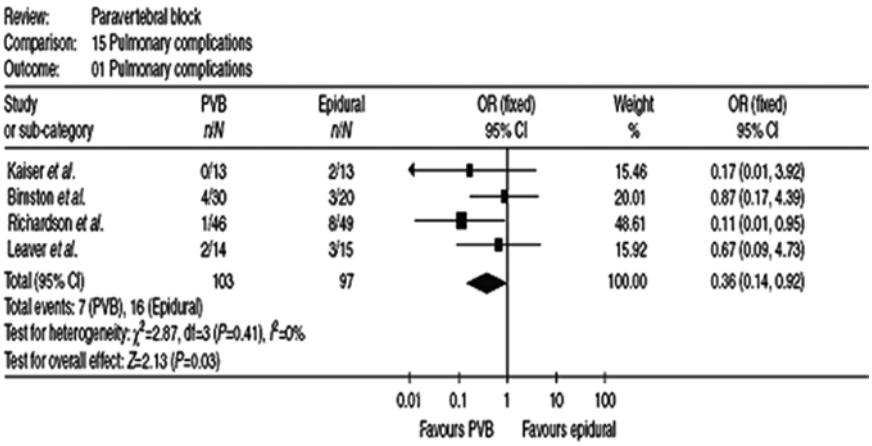


FIG. 46.1. A meta-analysis of trials comparing paravertebral block with thoracic epidural analgesia on postoperative pulmonary complications (reproduced from Davies et al. [11] by permission of Oxford University Press).

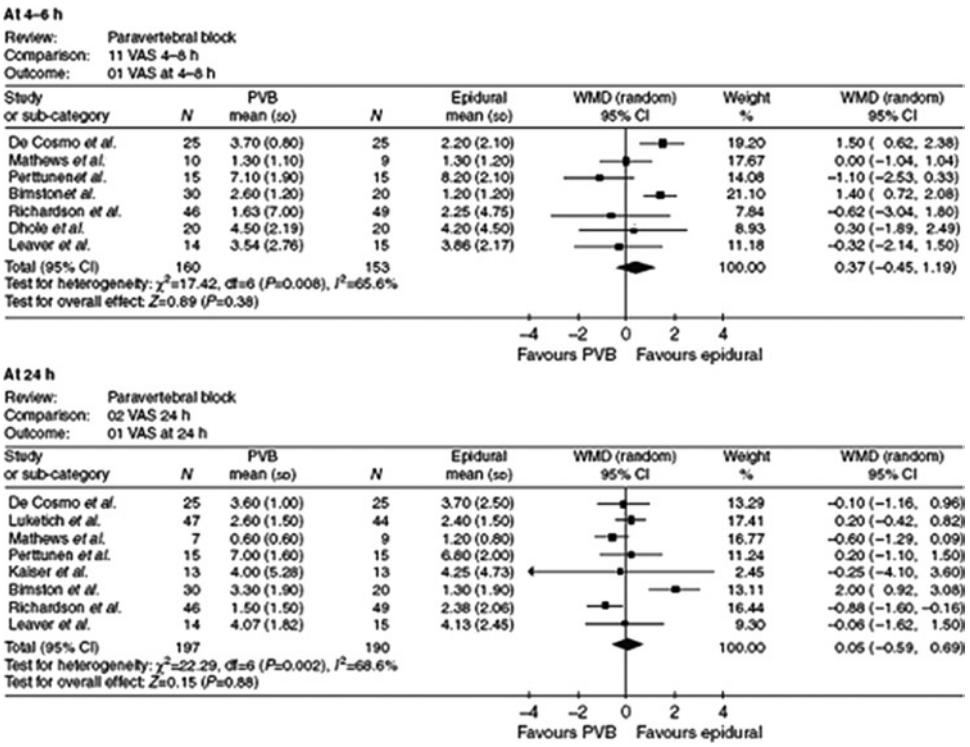


FIG. 46.2. A meta-analysis of trials comparing paravertebral block with thoracic epidural analgesia on visual analogue pain scores (reproduced from Davies et al. [11] by permission of Oxford University Press).

complications remains controversial. There is, however, a trend towards more openness. The understanding of informed consent has shifted with time. In the United Kingdom, at least, the standard is no longer what a body of reasonable practitioners would do but what a reasonable patient would expect. In 2001, the position was summarised "as part of the process of obtaining consent, except when they have indicated otherwise, patients should be given sufficient information about what is to take place, the risks, uncertainties, and possible negative consequences of the proposed treatments, about any alternatives and about the likely outcome, to enable them to make a choice about how to proceed" [13]. This change in the standard has resulted in a change in practice. Most anaesthetists now, for example, take specific consent for thoracic epidural analgesia [14]. Acute post-thoracotomy pain management aims to reduce the patient's pain as much as possible but to do so safely. In practice most patients undergoing thoracic surgery can be safely and effectively managed by thoracic epidural analgesia, paravertebral blocks or systemic opioids supplemented when appropriate by other systemic analgesics.

Pathophysiology of Post-thoracotomy Pain

The pathogenesis of post-thoracotomy pain is complex. Nociceptive receptors are stimulated by the skin incision, division and retraction of the muscles, retraction and sometimes fracture of ribs. In addition, ligaments may be stretched, costochondral joints dislocated and intercostal nerves injured, causing further pain. The incised pleura are frequently irritated by partial surgical stripping, chest drains and residual pleural blood; the resulting inflammatory responses activate further nociceptors. The central transmission of these multiple nociceptive signals amplifies pain transmission and increases pain perception through central sensitisation (see Fig. 46.3).

Without adequate treatment post-thoracotomy pain can be very severe and has been rated as near the top of a league of iatrogenic causes [15]. The surgical wound is subject to continuous movement as the patient breathes and ventilation is adversely affected. Inspiration stretches the injured structures initiating a reflex contraction of the expiratory muscles. Splinting of the injured hemi-thorax occurs to limit the distraction of the injured structures. Similarly, the usually passive expiration becomes active. Functional residual capacity falls usually to below the closing capacity and airway closure occurs. This can result in atelectasis, shunting and hypoxaemia. Deep inspiration is limited by pain, forced expiratory flow is thus reduced and effective coughing impaired. Sputum clearance is often adversely affected. Effective analgesia can reverse some of these changes and improve pulmonary function post-thoracotomy. There are, however, many other causes for the deterioration in pulmonary function that occurs post-thoracotomy. To date it has not been possible to determine with any accuracy the relative importance of pain in the aetiology of the changes in pulmonary function seen post-thoracotomy (see Table 46.1).

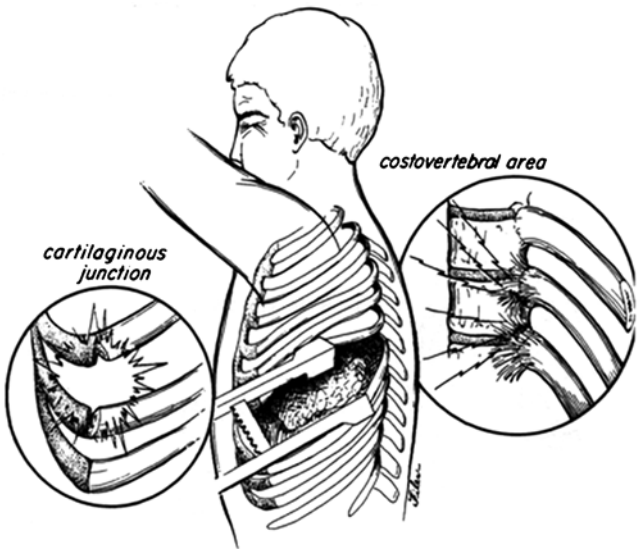


FIG. 46.3. Direct injury to ribs and neurovascular intercostals bundle along with injuries to anterior and posterior intercostals articulations during a thoracotomy (this figure was published in Landreneau et al. [276]. © Elsevier [1994]).

TABLE 46.1. Causes for deterioration in pulmonary function post-thoracotomy.

- Lung tissue resection
- Haemorrhage and oedema in residual lung tissue
- Distortion in bronchial architecture with resultant lobar collapse
- Gastric and abdominal distension
- Increased airway resistance
- Impaired mucocilary clearance
- Residual effects of anaesthesia
- Pain related changes in lung mechanics
- Diaphragmatic dysfunction

Reproduced with permission from Pennefather and Russell [279]

There are a number of mechanisms for transmitting the pain, generated post-thoracotomy, to the sensorium: Stimuli from the chest wall, costal and peripheral diaphragmatic pleura are transmitted via the intercostal nerves. Stimuli from the pericardium and mediastinuim are transmitted via the phrenic nerve. In addition, the vagus nerve contains somatic and visceral afferent nerve fibres and blockade of the vagus nerve has been advocated during thoracic surgery [16]. The sympathetic nerves may play a role in transmitting pain from the lung and mediastinum. It has been suggested that stretching of the brachial plexuses and distraction of the shoulder contributes to the pain in some patients [17].

Recent work has improved the understanding of mechanisms of post-thoracotomy pain. The phrenic nerve supplies sensory branches to the mediastinal pleura, to the fibrous pericardium, the parietal layer of the serous pericardium and diaphragmatic dome pleura. While well-managed thoracic epidurals provide excellent post-thoracotomy analgesia in the somatic dermatomes most patients still experience ipsilateral shoulder pain [18, 19]. In patient's receiving thoracic epidural

analgesia, the intra-operative blocking of the phrenic nerve at the level of the pericardial fat pad with local anaesthetic prevents ipsilateral shoulder pain in most, but not all patients [19]. Branches of the phrenic nerve to the pericardium or mediastinum arising proximal to the pericardial fat pad may account for the shoulder pain in some of the remaining patients. Supporting this hypothesis is the observation that patients in the above study who had undergone an intra-pericardial pneumonectomy and received a phrenic nerve block still experienced shoulder pain. An accessory phrenic is an alternative explanation. The ability of a combined phrenic nerve block and thoracic epidural to almost eliminate early post-thoracotomy pain [19] suggests that the contribution of the vagus nerve to post-thoracotomy pain may be minimal. In contrast, human vagal nerve stimulation can suppress pain [20]. Blocking the vagus nerve might actually increase post-thoracotomy pain by reducing vagally mediated central inhibition of pain.

Factors Influencing Pain After Thoracic Surgery

Pre-operative Preparedness

Well-informed patients may experience less pain [12] so whenever possible patients should receive a full explanation of the proposed analgesic technique and its likely effects including its limitations, potential side effects and complications.

Opioid Tolerance

Continuous opioid exposure results in a rightward shift of the dose–response curve to opioids resulting in patients requiring increased amounts of opioid to obtain the same pharmacological effect. It is a predictable pharmacological adaptation [21]. The degree of opioid tolerance is related to the dosage, duration and type of opioid administered. Opioid tolerance probably occurs because of decreased opioid receptor sensitivity and density [22], up-regulation of cyclic adenosine monophosphate [23] and neural adaptation [24]. Activation of *N*-methyl-D-aspartate (NMDA) receptors plays an important role in the development of opioid tolerance [25]. Opioid tolerant patients are relatively pain intolerant [26] and may have greater difficulty in coping with acute pain [27].

Pre-emptive Analgesia

The concept of pre-emptive analgesia was first suggested by Crile [28] although modern clinical interest is largely the result of basic science research done by Woolf [29]. Pre-emptive analgesia is anti-nociceptive treatment started before the noxious stimulus that aims to prevent the establishment of altered central processing of sensory input that amplifies post-operative pain [30]. Pre-emptive analgesia aims to decrease acute post-operative pain, even after the analgesic effects of the pre-emptive drugs have worn off, and to inhibit the development of chronic post-operative pain. Potential candidates for patients undergoing a thoracotomy include pre-incisional thoracic epidurals, paravertebral blocks, NMDA antagonists, gabapentin and systemic opioids. Although the results of clinical studies to support the concept of initiating the pain treatment prior to the injury are conflicting there is widespread belief in the concept amongst clinicians. A 2002 systematic review of pre-emptive analgesia for post-operative pain relief found no evidence of benefit for the pre-emptive administration of systemic opioids, non-steroidal anti-inflammatory drugs (NSAIDs) or ketamine and little evidence of benefit with continuous epidural analgesia [31]. A 2005 systemic review on the impact of pre-emptive epidural analgesia on pain after thoracotomy concluded that pre-emptive thoracic epidural analgesia was associated with a reduction in acute pain but no reduction in chronic post-thoracotomy pain [32].

Sex

A considerable amount of work has been undertaken in an attempt to determine the influence of the sex of the patient on the pain experienced after surgery. Female patients report pain to be more severe, frequent and diffuse than male patients with similar disease processes [33]. A meta-analysis of the influence of sex differences in the perception of noxious experimental stimuli, found that females were less tolerant of noxious stimuli than males [34]. The difference in pain perception between males and females decreases with age [35], has not been found by all investigators and is usually only moderately large. Social gender roles have a significant influence on pain tolerance levels [36], are sometimes difficult to differentiate from the sex of the patient and may account for some of the differences in pain tolerance between the sexes. Coping strategies also influence patient's pain tolerance; catastrophizing is associated with an increased sensitivity to experimental pain [37]. Women are more likely to catastrophize and this may help account for the differences in pain tolerance between the sexes [38]. Anaesthetists should be aware of the different responses male and female patients have to pain but as yet no specific recommendation with respect to treatment can be made.

Age

A recent systematic review found young age to be a significant predictor of post-operative pain [39]. The pharmacokinetics of analgesic drugs can be affected by ageing and the elderly are considered to be more sensitive to systemic opioids [40]. Similarly, there is a positive correlation between age and thoracic epidural spread with elderly patients requiring about 40% less epidural solution [41, 42]. It has also been suggested that age blunts peripheral nociceptive function decreasing

pain in some contexts [43] although this is not the experience of at least one ageing author.

Psychological Factors

Pain is a sensory and emotional experience and thus is influenced by psychological factors. It has been suggested that anxiety lowers pain thresholds [44]. Pre-operative anxiety has been shown to be a predictor of more severe post-operative pain in studies of patients undergoing a variety of surgeries including thoracic surgery [39, 45]. Good pre-operative communication with the patient and the development of rapport will facilitate reducing the anxiety by reassurance and, if appropriate, anxiolytics [39]. A depressive mood pre-operatively [46] and neuroticism [47] have also been found to be predictors of more severe post-operative pain. There may be a relationship between pre-operative depression and the development of chronic pain [48]. Cognitive factors can also influence pain perception. Catastrophizing, a multidimensional construct with elements of rumination, magnification and helplessness, has emerged as one of the most reliable predictors of heightened pain experience [37]. Cognitive behavioural strategies may have a role in managing patients who catastrophize about pain [39].

Surgical Approach

Sternotomy

The sternum is usually internally fixed with steel wire after a sternotomy. Bone movement during respiration is thus minimal and the post-operative pain usually only moderate. However, wide or inexpert distraction of the sternum may fracture the sternum, strain or even disrupt the anterior or posterior intercostal articulations with the potential to considerably increase the post-operative pain experienced.

Video-Assisted Thoracoscopic Surgery

With video-assisted thoracoscopic (VAT) surgery the extent of the surgical incision is limited and early post-operative pain can be reduced [49]. These benefits may be reduced by the use of larger-diameter instruments and/or the twisting of surgical instruments against the ribs causing injury to the intercostal nerves and bruising or even fracturing of the ribs.

Open Thoracotomy

Posterolateral Incision

Posterolateral incision is the classic approach to a thoracotomy as it provides good surgical access and can easily be extended if required. It does, however, involve the cutting of some of the major chest wall muscles and is considered one of the most painful surgical incisions. There is some evidence that internal fixation of divided ribs reduces post-operative pain [50].

Muscle-Sparing Incision

Many surgeons now use one or more of the many muscle-sparing incisions that have been described. A popular approach is the axillary muscle-sparing incision, the skin incision for which extends vertically downwards from the axilla with obvious cosmetic advantages. Although muscle sparing incisions were initially reported to produce less peri-operative pain [51–53] most studies have not found this reduction in peri-operative pain [54, 55]. Muscle-sparing incisions may result in less chronic post-thoracotomy pain [56]. Wider rib retraction is frequently required for muscle sparing thoracotomies to compensate for the reduced field of view [55]. Wider retraction may increase the risk of rib fractures, distraction of the posterior costovertebral joints and damage to the intercostal nerves, all of which can increase post-thoracotomy pain.

Anterior Incision

Anterior incisions are used to provide access for some cardiac and anterior mediastinal procedures. Exposure for lung surgery is, however, limited particularly on the left because of the heart. Rib resections are frequently performed with this incision to improve surgical access. Post-operative pain depends in part on the extent of the excision and the extent of surgical retraction but is similar to that after a posterolateral thoracotomy. Intercostal nerve blocks are particularly effective with this approach because the incision does not involve any part of the chest supplied by the posterior cutaneous nerves which arise from the dorsal rami and are not blocked by an intercostal nerve block (see intercostal nerve blocks).

Transverse Sternothoracotomy

Transverse sternothoracotomy (clamshell) incisions (see Fig. 46.4) provides excellent surgical exposure of both chest cavities and the mediastinum and were in the past used for cardiac surgery. This incision results in significant post-operative pain and its use is now largely limited to lung transplantation, complex cardiopulmonary surgery and complex mediastinal tumours [57]. Post-operative pain control can be challenging with this incision.

Analgesic Drugs and Techniques

Systemic Opioids

Systemic opioids were used in the past as the mainstay of post-thoracotomy analgesia; however, the pain control achieved was often poor. It is now appreciated that for open thoracotomies systemic opioids are best administered as part of a multimodal strategy including nerve blocks. Titration of systemic opioids post-thoracotomy is needed if the balance between the beneficial effects (analgesia, enabling passive expiration,

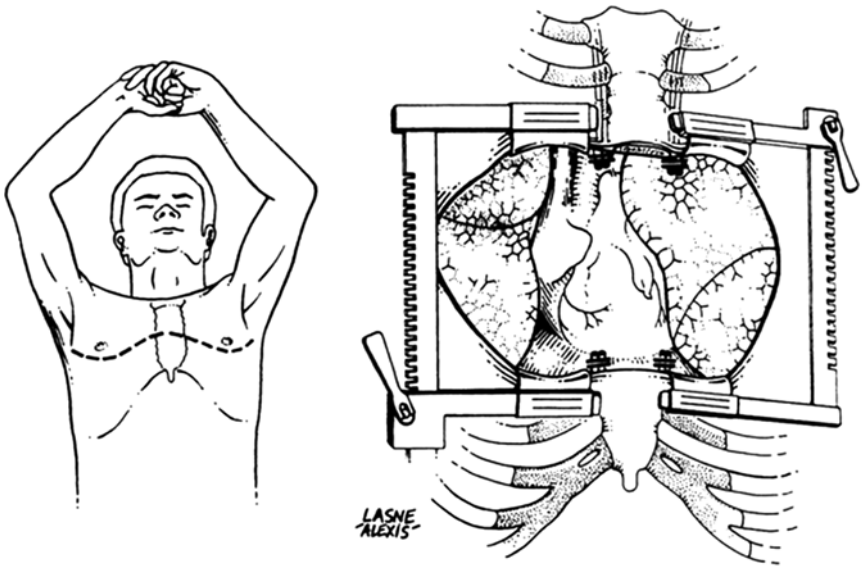


FIG. 46.4. Schematic view of a clamshell incision (this figure was published in Macchiarini et al. [57]. © Elsevier [1999]).

prevention of splinting) and detrimental effects (sedation and suppression of ventilation, coughing and sighing) is to be achieved. In comparison to IM opioids, IV-PCA systems provide superior analgesia [58] and improve patient satisfaction [59]. In part this is because IV-PCA systems accommodate the many-fold, between patient variation, in post-operative opioid requirement [60], the halving of opioid requirements approximately every 24 h post-operatively [61] and the small group of patients that experience minimal post-surgery pain [15]. A meta-analysis published in 1998 found that compared to systemic opioids, epidural local anaesthetic significantly reduced the incidence of pulmonary complications after surgery [62]. This finding was not, however, supported by a systematic review published in 2008 [10]. Perhaps this was because of improvements in the administration of systemic opioids in later studies included in the second review. Recent studies suggest acute exposure to opioids can lead to the development of acute opioid tolerance [63].

Non-opioid Analgesic Drugs

Non-steroidal Anti-inflammatory Drugs

Prostaglandins have a role in pain perception. NSAIDs block the synthesis of prostaglandins by inhibiting the enzyme cyclo-oxygenase. NSAIDs reduce the inflammatory response to surgical trauma, have a peripheral non-prostaglandin analgesic effect [64] and act centrally [65] in part by inhibiting prostaglandin synthesis in the spinal cord [66]. The side effects of NSAIDs are well known and include gastrointestinal mucosal damage [67], renal tubular and platelet dysfunction [68]. The amount, if any, of NSAID mediated increased bleeding after thoracotomy has not been established, although studies after tonsillectomy suggest that the increased bleeding is probably minimal [69]. Renal failure is a particular risk for elderly patients undergoing major surgery [70, 71], patients with pre-existing renal failure and hypovolaemic patients. These risk factors are often present in patients scheduled for thoracic surgery. There is a concern that NSAID-mediated reductions in inflammation may reduce the efficacy of a surgically performed pleurodesis. For more than 25 years, NSAIDs have been used to control post-thoracotomy pain [72]. NSAIDs have been shown to significantly improve pain control in patients receiving systemic opioids post-thoracotomy [73, 74]. NSAIDs have not been shown to significantly reduce pain scores in patients receiving thoracic epidural analgesia post-thoracotomy [75]. NSAIDs may be effective in controlling the ipsilateral shoulder pain post-thoracotomy in patients receiving thoracic epidural analgesia [18, 76], although research in this area has been limited.

COX-2 Inhibitors

Different isoenzymes of the cyclo-oxygenase enzyme exist including COX-1 and COX-2 [77]. The COX-1 isoenzyme has physiological functions while the COX-2 isoenzyme is induced during inflammation. NSAIDs vary in their selectivity for inhibiting these cyclo-oxygenase isoenzymes. Some are selective cyclo-oxygenase 2 inhibitors and are termed COX-2 inhibitors. These agents have a lower risk of causing serious upper gastrointestinal side effects and cause less platelet inhibition than the non-selective NSAIDs. There is some evidence that COX-2 inhibitors may limit the development of acute opioid tolerance [78]. There are concerns about the detrimental effects of COX-2 inhibitors (and NSAIDs) on bone growth [79, 80]. In 2004/2005, two COX-2 inhibitors (rofecoxib and valdecoxib) were withdrawn because of concerns that there was an increased risk of cardiovascular thrombotic complications when these agents were taken daily for long periods. Subsequent studies support this finding as being a COX-2 (and non-selective NSAID) class effect [81, 82]. Caution is required if these drugs are to be administered regularly

over long periods. The safety of COX-2 inhibitors in the peri-operative setting is controversial. For patients undergoing CABG on cardiopulmonary bypass there is an increased risk of cardiovascular thrombotic events in patients receiving the selective COX-2 inhibitors parecoxib/valdecoxib [83, 84]. A study of a variety of non-cardiac surgical procedures including thoracic surgery did not show an increased incidence of cardiovascular thrombotic events in patients receiving the selective COX-2 inhibitors parecoxib/valdecoxib [85]. The level of cardiovascular risk associated with the short-term peri-operative use of COX-2 and NSAIDs remains controversial. For individual patients, their cardiovascular risk factors and the risks of alternative drugs or analgesic techniques need to be considered. The cardiovascular risk between agents varies, for example the NSAID naproxen has a lower cardiovascular risk profile than diclofenac [86].

Acetaminophen

Acetaminophen, perhaps the safest of the non-opioid analgesic agents, acts centrally by inhibiting prostaglandin synthesis [87] and possibly via the serotoninergic system [88]. Acetaminophen may also have peripheral anti-inflammatory actions [89]. A recent meta-analysis found that after major surgery adding acetaminophen to morphine PCA reduced the morphine consumption by 20% but did not decrease the incidence of morphine-related adverse effects [90] (see Fig. 46.5).

There is some evidence that the effects of acetaminophen and NSAIDs are additive [91, 92]. Regular rectal acetaminophen has been shown to reduce the severity of ipsilateral post-thoracotomy shoulder pain [93]. When administered rectally the dosage should exceed the oral dose by 50%, and account should be taken of its slower onset [94]. Propacetomol, a prodrug that is hydrolysed to acetaminophen by plasma esterases, can be administered intravenously. Propacetomol has been shown to decrease morphine consumption after spinal [95] and cardiac surgery [96] although a reduction in morphine consumption after cardiac surgery was not shown in an earlier study, possibly because of the methodology [97].

Unlike NSAIDs and COX-2 inhibitors, acetaminophen at clinical doses has few contraindications or side effects. It is considered safe for patients at risk of renal failure [94]. Acetaminophen is frequently administered post-thoracotomy [3].

NMDA Antagonists

Ketamine, an anaesthetic with analgesic properties, is a non-competitive antagonist of the phencyclidine site of the NMDA receptor. Ketamine is now infrequently used for the induction or maintenance of anaesthesia because of its side effects particularly the psychomimetic effects. There is now, however, renewed interest in the use of small doses of ketamine as an adjuvant to post-operative analgesia. Activation of spinal NMDA receptors plays an important role in the development of central neuron sensitisation causing the behavioural manifestations of pain [98]. NMDA receptor antagonists enhance opioid-induced analgesia and can limit the development of opioid tolerance [98, 99]. Small doses of ketamine have been shown to have opioid sparing effects after abdominal surgery [100]. In a double-blind study of patients who had undergone thoracic surgery adding ketamine to morphine delivered via an IV-PCA system reduced morphine consumption and improved the early post-operative FEV_1 [101]. In another study, adding a low dose intravenous infusion of ketamine to thoracic epidural analgesia improved early post-thoracotomy analgesia [102]. The post-operative use of ketamine should be considered for some patients, for example patients chronically receiving high dose opioids.

Gabapentin

Gabapentin, 1-(aminomethyl)cyclohexane acetic acid, is an anticonvulsant drug that is effective in treating neuropathic pain [103] and post-herpetic neuralgia [104]. Gabapentin may act through a number of mechanisms. The most likely site of its anti-nociceptor effect is thought to be by binding to the $\alpha_2\delta$ subunit of voltage-dependent calcium channels [105]. The absorption of gabapentin is dose dependent. In the United

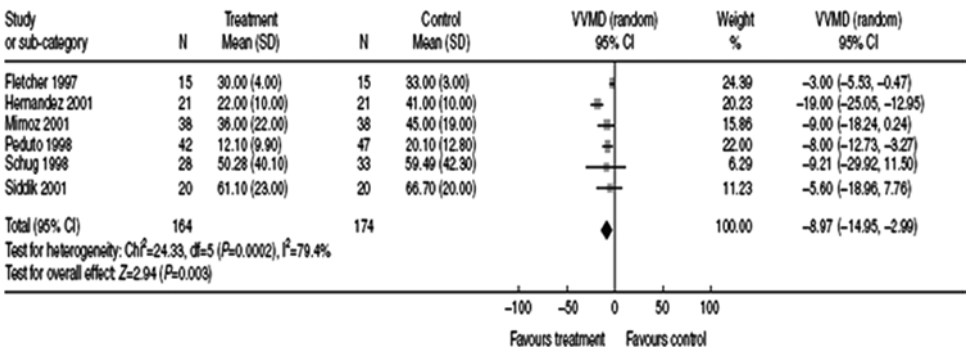


FIG. 46.5. Effect of acetaminophen on postoperative morphine consumption during the first 24 h after major surgery (reproduced from Remy et al. [90] by permission of Oxford University Press).

Kingdom, gabapentin has a product licence for the treatment of neuropathic pain. Because of its mechanism of action and effectiveness in neuropathic states its effectiveness in preventing chronic post-surgical pain has been investigated. There is as yet no clinical evidence that it reduces chronic post-surgical pain [106]. The use of gabapentin for acute peri-operative pain is "off-label". There is good evidence that gabapentin reduces early postoperative pain scores and reduces the opioid consumption in the first 24 h for patients undergoing a variety of surgical procedures [107]. Gabapentin has been administered as a single pre-operative oral dose ranging from 300 to 1,200 mg and as multiple peri-operative doses. No additional pain reduction or opioid sparing effect was detected when multiple peri-operative doses were administered and therefore for practical purposes a single pre-operative dose of 1,200 mg or less is recommended [106]. Gabapentin is sedative and anxiolytic [108], and the doses of other premedication drugs used should be adjusted accordingly. In a placebo-controlled study, gabapentin did not decrease ipsilateral shoulder pain in patients receiving thoracic epidural analgesia [109]. Pre-operative gabapentin use should be considered in patients in whom difficulties in controlling post-thoracotomy pain are anticipated, for example patients undergoing thoracotomy in whom local anaesthetic blocks are not scheduled, and opioid tolerant patients.

Glucocorticoids

Glucocorticoids (dexamethasone) have many actions including analgesic, anti-emetic, anti-pyretic and anti-inflammatory effects. Reduced prostaglandin production by the inhibition of phospholipase and COX-2 isoenzymes is believed to be the major pathway for the analgesic effect. Dexamethasone has been shown to produce a dose-dependent opioid sparing effect [110] in a general surgical setting, and has been particularly effective in reducing pain scores with dynamic movement [111, 112]. The onset of analgesia is slower than traditional analgesics but appears to last longer and has been reported to last for up to 7 days [113]. These effects have been produced with a single dose of dexamethasone within the range of 10–40 mg with few reported serious side effects. Risks of glucocorticoid use include gastric irritation, impaired wound healing, impaired glucose homeostasis and sodium retention. The optimal dose that balances the advantages against these, and other, risks has yet to be defined and further research, particularly in the setting of thoracic surgery is required. If difficulties with post-thoracotomy pain control are anticipated and there are no contraindications to glucocorticoid use, selected patients may benefit from a single 10–16 mg dose of dexamethasone as part of a multimodal analgesia regime.

Non-pharmacologic Techniques

Transcutaneous Nerve Stimulation

Transcutaneous nerve stimulation (TENS) was developed to utilise the gate theory to reduce pain [114]. A meta-analysis published in 1996 of the effectiveness of TENS in acute post-operative pain found little evidence for effectiveness in adequately randomised studies [115]. In contrast, TENS was considered by the original authors to be effective in most of the non-randomised studies analysed [115]. Seven studies have examined the effectiveness of adding TENS to post-thoracotomy analgesia regimens [116–122]. Some studies were not adequately randomised [117] and others inadequately blinded [116]. When appropriately analysed, most of the remaining studies did not show a significant benefit [118–120]. Although not recommended, TENS may possibly be of some benefit after VAT surgery [120].

Cryoanalgesia

While the chest is open the intercostal nerves can be blocked for up to 6 months by the application of a cryoprobe. The analgesia is inferior to thoracic epidural fentanyl [123] and the technique is associated with an increased incidence of chronic post-thoracotomy pain [124]. Cryoanalgesia is now rarely used to provide post-thoracotomy analgesia and cannot be recommended.

Specific Techniques

Continuous Wound Infiltration Catheters

Randomised studies have shown that delivering local anaesthetic into the wound via catheters placed prior to closure can reduce post-operative opioid use [125] and may reduce wound oedema [126]. For patients receiving continuous paravertebral infusions, the potential for local anaesthetic toxicity usually makes this technique inappropriate. For patients receiving thoracic epidural analgesia, this technique is usually unnecessary. It should, however, be considered for patients not scheduled to receive local anaesthetic infusions by other routes for post-operative pain control.

Intercostal Nerve Blocks

The spinal nerves divide into a dorsal and ventral ramus. The upper eleven thoracic ventral rami form the intercostal nerve which runs forward between the ribs in the intercostal spaces. Each intercostal nerve gives off a lateral cutaneous branch that pierces the intercostal muscles proximal to the posterior axillary line to supply the lateral aspect of the chest wall. It is important therefore the intercostal nerves are blocked proximal to the posterior axillary line to ensure that the lateral cutaneous branches and thus the lateral aspect of the chest wall are blocked. The thoracic dorsal rami pass backwards close to the vertebrae to supply the cutaneous innervation to the back. The dorsal rami are not blocked by an intercostal nerve block. This limits the effectiveness of intercostal nerve blocks for posterolateral thoracotomies (see Fig. 46.6).

The intercostal nerves can easily be blocked under direct vision while the chest is open but because of the relatively

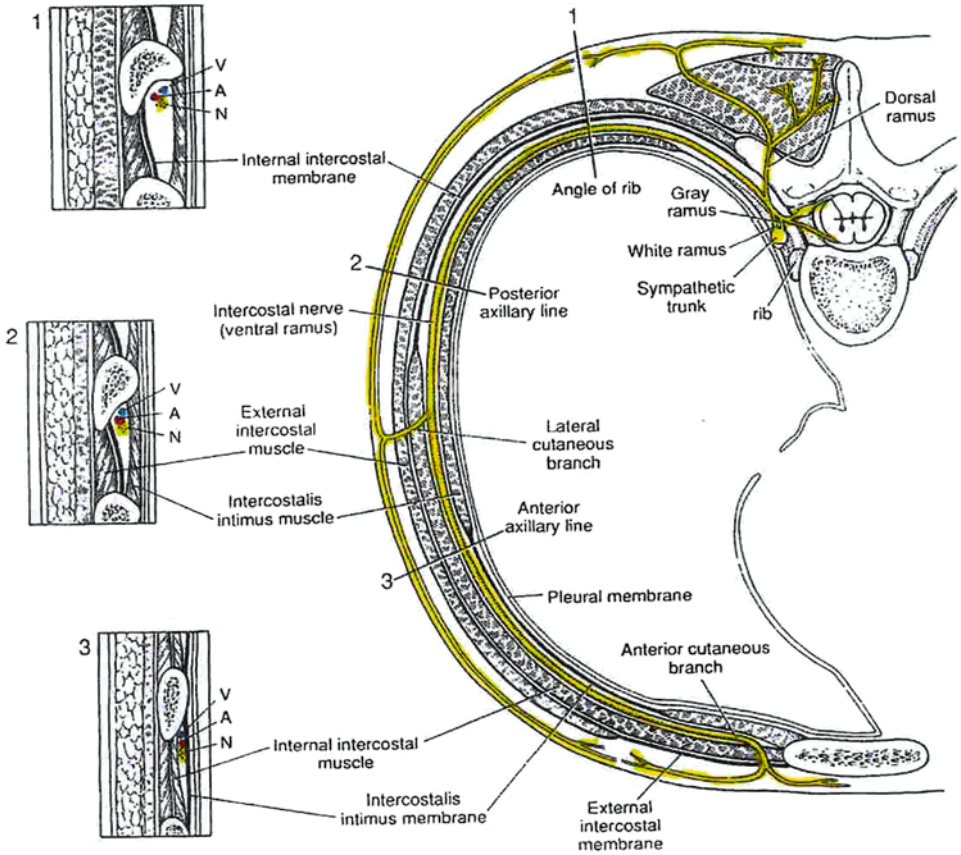


FIG. 46.6. Anatomy of intercostal nerve and space (reproduced with permission from Dravid and Paul [131]. © Blackwell Publishing Limited [2007]).

short half-life of most local anaesthetics repeated percutaneous blocks are usually required. The intercostal nerves consistently lie in a plane deep to the internal intercostals muscle although there is considerable variability in the position of intercostal nerves within the intercostal spaces [127]. Small (5 mL) bolus of local anaesthetic deposited in the correct plane will block the appropriate intercostal nerve. Larger doses may also block adjacent intercostal nerves by spreading medially to the paravertebral space or directly to the adjacent spaces (see Fig. 46.7). The systemic uptake of local anaesthetic from the highly vascular intercostal space is rapid and the dose of local anaesthetic administered by this route needs to be appropriately limited. Intercostal nerve blocks significantly reduce post-operative pain and analgesic requirements post-thoracotomy [128–130].

Interpleural Blocks

In healthy human adults, the two layers of the pleura have a surface area of about 0.2 m^2, are separated by a distance of 10–20 μm and contain approximately 10 mL of pleural fluid [131]. The deposition of local anaesthetic between the parietal and visceral pleura with the aim of producing an ipsilateral somatic block of multiple thoaracic dermatomes constitutes an interpleural block and was originally described by Kvalheim and Reiestad [132]. Unfortunately, the terminology used in the literature to describe this block can be confusing, some authors use the term intrapleural block [133] and others pleural block [134]. The issue is further confused when the term interpleural block is used to describe a paravertebral block [135]. Although studies have consistently shown interpleural blocks to be effective for pain relief after cholecystectomy [135] most studies of patients undergoing a thoracotomy have shown interpleural blocks to be ineffective [136–139]. The wide spread of local anaesthetic within the normally small (10 mL) pleural space is aided by surface tension forces and this probably accounts for the effectiveness of interpleural blocks after cholecystectomy. After thoracotomy the volume of the pleural space is much larger and contains blood and air. The effect of surface tension forces is reduced and the spread of local anaesthetics is limited and principally via gravity. Dilution of the administered local anaesthetic by interpleural blood [140] and the loss of local anaesthetic into the chest drains [139–141] further reduce the efficacy of this technique. A possible role for interpleural bupivacaine, administered post-thoracotomy via the basal chest drain, to reduce local diaphragmatic irritation from the basal chest drain was explored in a double-blind study. Interpleural local anaesthetic administered by this route was found to be ineffective [142]. Systemic absorption of interpleurally administered local anaesthetic can be considerable and high

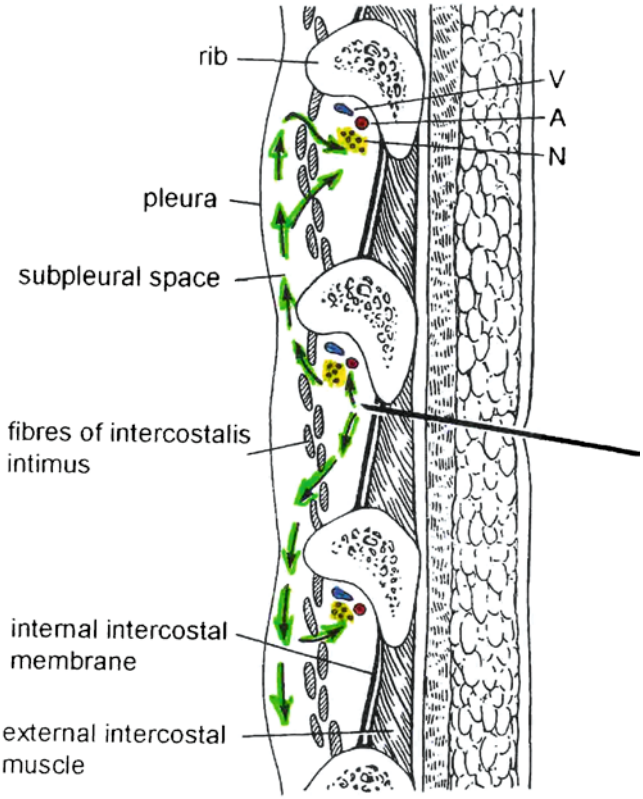


FIG. 46.7. Intercostal nerve block. Showing spread of local anaesthetic to adjacent spaces (*arrows*) (reproduced with permission from Dravid and Paul [131]. © Blackwell Publishing Limited [2007]).

plasma levels of local anaesthetics have been reported [138]. Interpleural blocks are not recommended for post-thoracotomy analgesia in adults [10].

Paravertebral Blocks

Paravertebral blocks were introduced into clinical practice in 1906 [143] and were then largely abandoned before being reintroduced in 1979 [144]. There has now been substantial experience in the use of thoracic paravertebral block for thoracic surgery and their safety has been established. Continuous thoracic paravertebral blocks can provide excellent post-thoracotomy analgesia and a number of studies have shown that the analgesia is comparable to that provided by thoracic epidurals but with fewer complications [11]. Not all clinicians, however, are able to get reliably good analgesia with paravertebral blocks. Paravertebral block failures may occur for a number of reasons including failure to place or maintain the catheter in the paravertebral space, failure to contain the local anaesthetic solution within the paravertebral space and failure to deposit local anaesthetic at the appropriate level or extend the block over sufficient dermatomes to provide adequate analgesia. Although it is possible to blindly place catheters percutaneously into the paravertebral space it is often more appropriate for the surgeon to insert the catheter into the paravertebral space under direct vision while the chest is open. Direct placement facilitates advancement of the catheter along the paravertebral space to create a narrow longitudinal pocket that will block sufficient dermatomes to provide adequate analgesia.

Anatomy

The paravertebral space is a potential space. At the thoracic level the paravertebral space is a wedge-shaped area bounded posteriorly by the costo-transverse ligaments, transverse processes and necks of the ribs (see Fig. 46.8). Medially it is bound by the vertebral bodies, discs and intervertebral foramina. The anterior border of the space is formed by the parietal pleura. Lateral to the tips of the transverse processes the paravertebral space is continuous with the intercostal neurovascular space (see Fig. 46.9).

The paravertebral space is contiguous with the paravertebral spaces above and below. The caudal boundary is formed by the psoas major muscle [145], the cranial boundary is, however, not well defined [146]. The thoracic paravertebral space is divided into an anterior subpleural paravertebral compartment and a posterior subendothoracic paravertebral compartment by the endothoracic fascia which is the deep fascia of the thorax [146] (see Fig. 46.10). Contained within the paravertebral space are the dorsal and ventral rami of the spinal nerves, the grey and white rami communicans and the sympathetic chain. The intercostal nerves (ventral ramus) are devoid of a fascial sheath within the paravertebral space making them highly susceptible to local anaesthetic block at this site [147].

Methods of Performing Paravertebral Blocks

The relatively short duration action of clinically available local anaesthetics makes single bolus paravertebral blocks inappropriate for most post-thoracotomy patients. Paravertebral blocks are best established with a bolus of local anaesthetic and maintained with a constant infusion of local anaesthetic via a catheter placed in the paravertebral space. Ultra long-acting local anaesthetic agents are being developed and placement of these agents in the paravertebral space may in the future make single bolus paravertebral blocks practical and thereby reduce the risks of local anaesthetic toxicity and block failure because of catheter displacement. Biodegradable bupivacaine-containing polymer microcapsules can produce prolonged local anaesthesia [148], adding a glucocorticoid prolongs the effect further [149]. In sheep the granulomatous reactions that occurred around the bupivacaine microcapsules can be prevented by adding dexamethasone [150]. Bupivacaine–dexamethasone microcapsules have been shown to produce an intercostal nerve block of up to 4 days duration in humans [151]. Bupivacaine has also

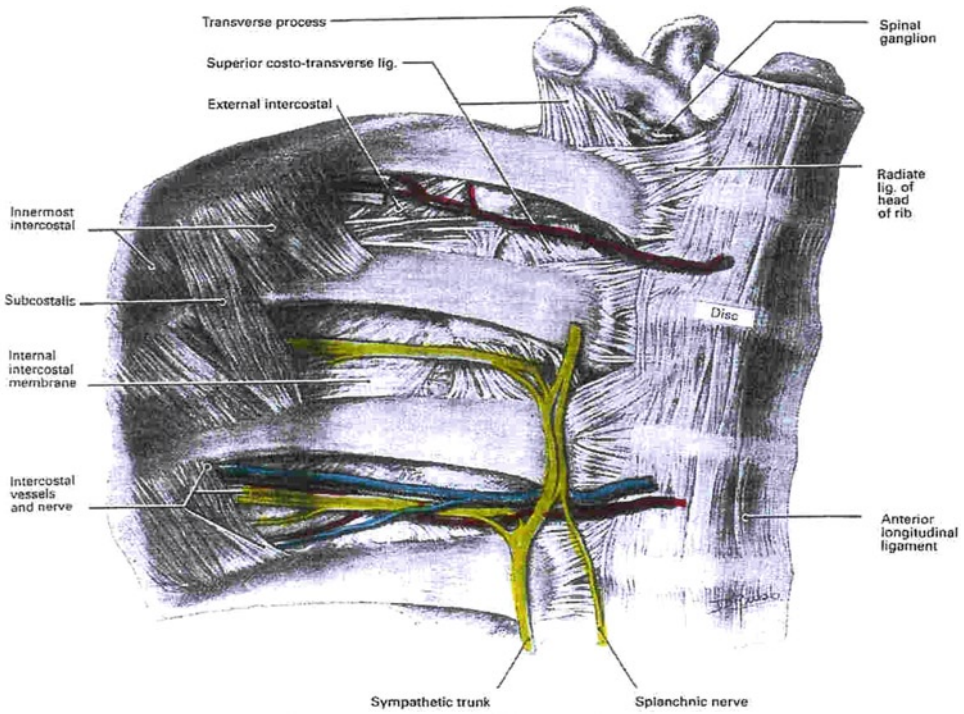


FIG. 46.8. Posterior relations of the thoracic paravertebral space (reproduced from Murphy [135] by permission of Oxford University Press).

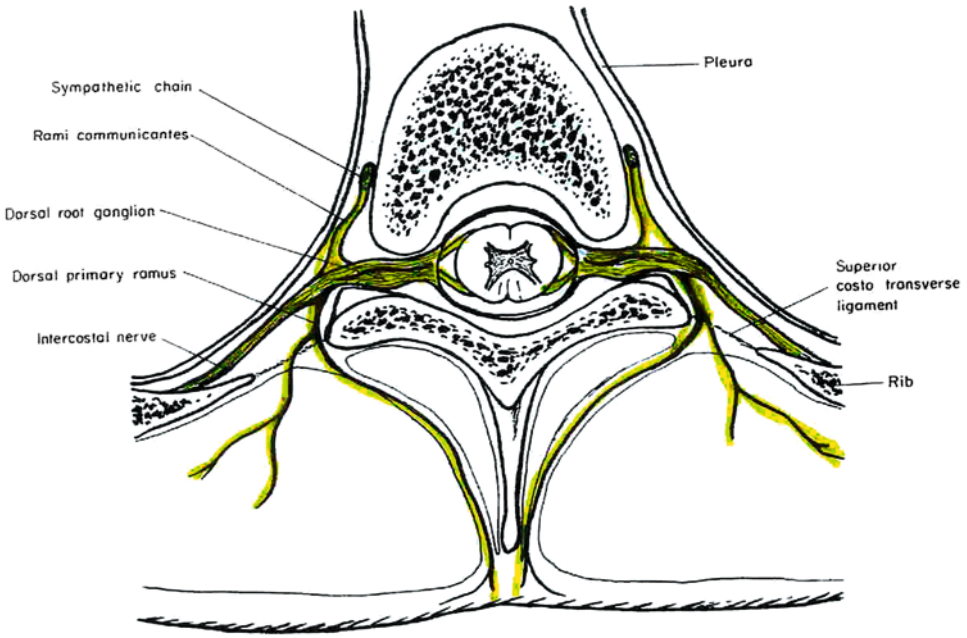


FIG. 46.9. Transverse section at the level of the intervertebral foramen showing the paravertebral spaces (reproduced with permission from Eason and Wyatt [144]. © Blackwell Publishing Limited [1979]).

been incorporated into liposomes [152]. Liposomal bupivacaine has a prolonged action in animals [153] and has been used to provide post-operative epidural analgesia in humans [154]. Recently, an absorbable local anaesthetic matrix has been used in rats [155].

Percutaneous Methods

A number of different techniques for the percutaneous placement of paravertebral catheters have been described. Perhaps the most widely used technique is the one described

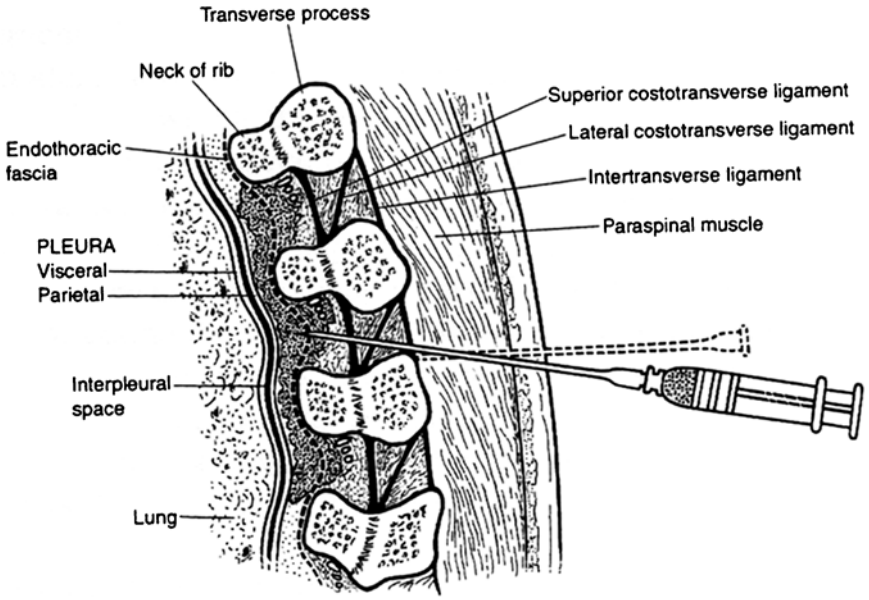


FIG. 46.10. Saggital section through the paravertebral space showing a needle that has been walked off the transverse process (reproduced from Karmakar [146] with permission).

by Eason and Wyatt [144]. For the Earson technique, a Tuohy needle is inserted 3 cm lateral to the cranial edge of a spinous process at the appropriate level. The needle is then advanced perpendicular to the skin until contact is made with the underlying transverse process. If contact with bone is not made at the expected depth the needle is withdrawn and then re-advanced slowly, while fanning it in the sagittal plane, until contact with bone is made. The needle is then walked off the cranial edge of the transverse process and advanced slowly until a loss of resistance, less complete than that in the epidural space, is encountered, usually after a further 1 cm. This is frequently preceded by a subtle click as the costotransverse ligament is penetrated. In adults after aspiration, to confirm the needle is extravascular, approximately 20 mL of an appropriate local anaesthetic (e.g. 0.25% levobupivacaine) is administered to open up the paravertebral space before threading an epidural catheter into the paravertebral space. Consideration may be given to adding a small quantity of dye to the local anaesthetic administered, so correct placement of the block can be confirmed visually at subsequent thoracoscopy or thoracotomy.

An alternative technique whereby the paravertebral space is approached from an intercostal space has recently been described [156]. A Tuohy needle is positioned posteriorly over a rib at the appropriate level about 8 cm lateral to the head of that rib and advanced until contact is made with the rib. The needle is then orientated so the bevel is pointing medially and the tip is angulated 45° cephalad and 60° medial to the sagittal plane. The needle tip is then walked off the inferior border of the rib while maintaining this orientation and advanced a few millimetres until loss of resistance confirms that the intercostal neurovascular space has been entered. After aspirating to confirm the needle is extravascular approximately 5 mL of 0.25% levobupivacaine is injected to open up the intercostal neurovascular space. An epidural catheter is then inserted into the Tuohy needle and advanced into the intercostal neurovascular space. The orientation of the needle directs the catheter along the intercostal neurovascular space towards the paravertebral space. The catheter is inserted about 8 cm into the intercostals space so the tip lies in the paravertebral space [156]. Percutaneous thoracic paravertebral blocks are technically simple to perform but have a failure rate of up to 10%. The use of ultrasound guidance may result in reduced failure rates. Failure rates can also be reduced by direct surgical placement.

Open Methods

Direct placement techniques may require some surgical preplanning. The posterior extent of the incision needs to be limited to allow sufficient room for the paravertebral. In particular it is important to preserve enough pleura posterior to the surgical incision. Direct placement techniques are usually undertaken at the end of surgery immediately prior to closure to reduce the risk of inadvertent catheter dislodgement. The direct placement of catheter into the paravertebral space at the end of surgery was first popularised by Sabanathan et al. [157]. They described a technique whereby a catheter is inserted via a Tuohy needle. The catheter is inserted percutaneously medial to the posterior edge of the thoracotomy incision to emerge between the angle of the ribs into the chest cavity. The parietal pleura two spaces above and below the incision is peeled back medially to expose the intercostal nerves taking care not to perforate the pleura. The catheter is then positioned to lie against the angles of the exposed ribs before the parietal pleura is reattached to the posterior aspect of the wound. The authors later reported an improvement in their technique [158]. After reflecting back the parietal pleura to the vertebral bodies as before, a small incision is made in the endothoracic fascia and the catheter is passed into the subendothoracic paravertebral

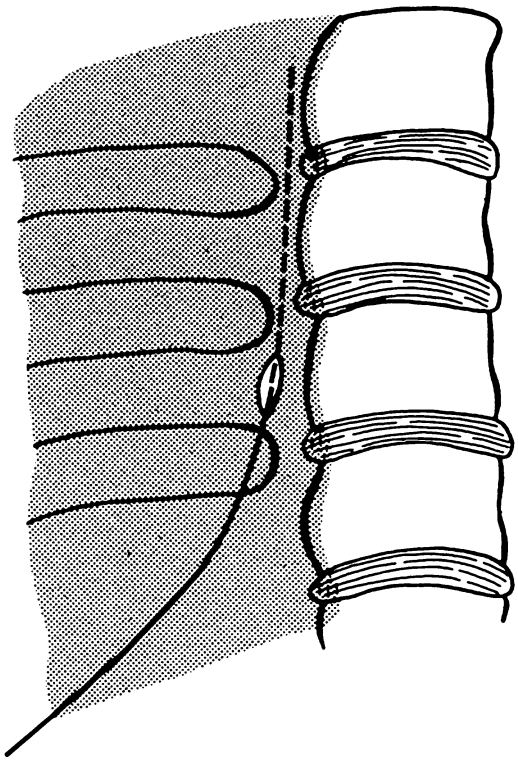


FIG. 46.11. A technique for performing paravertebral blocks. The endothoracic fascia (stippled) is exposed by raising the parietal pleura from the posterior chest wall. A catheter is inserted deep to the endothoracic fascia through a small hole created in the fascia (this figure was published Berrisford and Sabanathan [158]. © Elsevier [1990]).

compartment and advanced cranially for a few centimetres, aided if necessary by blunt dissection. The hole in the endothoracic fascia is then closed by a suture (see Fig. 46.11).

Another technique used in the author's institution is for the surgeon to insert a Tuohy needle percutaneous, under direct vision, into the paravertebral space one or two segments caudal to the thoracotomy incision. A catheter is then introduced through the Tuohy needle and advanced 10 cm or more cranially in the paravertebral space. This requires careful manipulation of the Tuohy needle and catheter to ensure it advances in the correct direction and damage to the overlying pleura is avoided. The other end of the catheter can then be tunnelled subcutaneously to limit the risk of inadvertent dislodgement. For patients undergoing video-assisted surgery, video-assisted surgical placement of a catheter is possible [159].

Management of Paravertebrals

The appropriate management of paravertebrals (drug choice, rate, adjuvant and administration technique) has not yet been established and further work is required to optimise the efficacy and safety of this technique. A review and meta-regression analysis [160] found that a higher bupivacaine dose (890–990 mg per 24 h) predicted lower pain scores and faster recovery of pulmonary function compared to lower dose (325–472.5 mg) without a significant difference in the rate of local anaesthetic toxicity. Continuous infusions were associated with significantly lower pain scores than intermittent boluses while the addition of adjuvants, fentanyl or clonidine, did not improve the analgesia. The use of safer local anaesthetic, such as levobupivacaine, vigilance for signs and symptoms of local toxicity (confusion), the addition of adrenaline to the solution and reducing the infusion rate for elderly or frail patients may all be appropriate steps to reduce the incidence of toxicity with the use of paravertebrals. A typical dosing regime for an adult patient might be 0.3 mL kg^{-1} initial bolus of 0.25% levobupivacaine followed by a 0.1 mL kg^{-1} h^{-1} infusion of 0.25% levobupivacaine (see Table 46.2).

Limitations and Complications of Paravertebral Blocks

To provide effective analgesia in the affected somatic dermatomes, post-thoracotomy paravertebral blocks may need to cover up to ten segments. It usually takes a number of hours for the local anaesthetic to spread sufficiently along the paravertebral space and as a result the early post-operative analgesia may be poor unless supplemented initially by other analgesic agents or techniques. Complications that have been reported include inadvertent pleural puncture, pulmonary haemorrhage, inadvertent dural puncture, hypotension, nerve injury and central nervous system local anaesthetic toxicity. The incidence of these complications is low but the available published data does not enable an exact incidence to be quoted to patients [146]. Many of the potential complications of paravertebrals can be greatly reduced, if not eliminated, by using an open method of insertion. However, the large volume of local anaesthetic required and rapid uptake of local anaesthesia from the vessel-rich paravertebral space mean that local anaesthetic toxicity is a concern. Mean plasma concentrations have been shown to exceed the threshold for central nervous system toxicity 48 h after commencing a 0.1 mL kg^{-1} h^{-1} infusion of 0.5% bupivacaine [161]. In a separate study of patients receiving paravertebral 0.5% bupivacaine at this rate, 7% of patients developed temporary confusion attributed to bupivacaine accumulation [162]. Until recently, there has been no specific treatment available for local anaesthetic toxicity. There is now a growing body of evidence from animal studies and case reports that lipid emulsion given intravenously improves outcome. It is therefore recommended that lipid emulsion is available wherever patients receive large doses of local anaesthetic such as for a paravertebral block. The management of local anaesthetic toxicity induced cardiovascular collapse should involve CPR as per standard protocols followed by the consideration to administer a lipid emulsion [163, 164]. To put the risks in perspective, no fatality directly related to thoracic paravertebral block had been reported by 2001 [146].

Table 46.2. Adult analgesic regimes.

Technique	Dose	Comment
Paravertebrals		
Lower dose regime		
Loading dose	0.3 mL kg^{-1} 0.25% Levobupivacaine	Higher dose regime produces improved analgesia and pulmonary function [160]
Maintenance	0.1 mL kg^{-1} h^{-1} 0.25% Levobupivacaine	
High dose regime		
Loading dose	20 mL 0.5% Levobupivacaine	
Maintenance	0.1 mL kg^{-1} h^{-1} 0.5% Levobupivacaine	
Intrathecal opioids	Morphine 200 µg + sufentanil 20 µg [166] or morphine 500 µg + sufentanil 50 µg [167]	
Thoracic epidural		
Levobupivacaine	0.1%	Titrate to effect
or		
Ropivacaine	0.15%	Reduce rate by 40% for elderly
with		
Fentanyl	4–5 µg mL^{-1} or	
Sufentanil	1 µg mL^{-1} or	
Hydromorphine	10–25 µg mL^{-1} [280]	
Bolus	7 mL	
Infusion	7 mL h^{-1}	
Intercostal nerve blocks		
Injection sites T3–T7	0.25% Levobupivacaine with epinephrine 1:200,000 3–5 mL per site	Use repeated doses or continuous infusion [10]. Associated with rapid absorption of local anaesthetic
Ketamine		
For intravenous supplementation of epidural analgesia	0.05 mg kg^{-1} h^{-1} [102]	
Without epidural analgesia		
Bolus	0.5 mg kg^{-1} [274]	
Infusion	4 µg kg^{-1} min^{-1} Continued for few days [274]	
Gabapentin	300–1,200 mg Orally 1–2 h pre-operatively [106]	No benefit from multiple post operative doses [106]

Advantages of Paravertebral Analgesia

Paravertebral block is a relatively simple technique that is easy to learn, has few contraindications and has a low incidence of complications. The open technique enables paravertebral blocks to be safely initiated in anaesthetised patients. This makes the technique particularly appropriate for patients in whom a VAT procedure is converted to an open thoracotomy. Impaired coagulation is a relative contraindication to the percutaneous insertion of paravertebrals. However, for patients with impaired coagulation open placement is relatively safe and can be recommended. Hypotension, urinary retention, nausea and vomiting are less frequent post-operatively with paravertebrals than with thoracic epidurals [11]. In the author's institution, paravertebrals are associated with earlier mobilisation and shorter hospital stays than thoracic epidurals.

Intrathecal Analgesia

The lumbar administration of subarachnoid opioids is an infrequently used technique that may have a wider role in providing post-thoracotomy analgesia. The use of intrathecal morphine to provide operative analgesia was first described in 1979 [165]. Since then a number of studies have reported the use of intrathecal opioids for post-thoracotomy analgesia [166–172]. The onset time of intrathecal opioids depends in part on their lipid solubility [173]. With intrathecal sufentanyl the onset of analgesia is very rapid whereas morphine has a slower onset but longer duration of action. Combinations of morphine and sufentanyl have been used to provide post-thoracotomy analgesia. In one study, morphine 200 µg was combined with sufentanyl 20 µg [166] in another study morphine 500 µg was combined with sufentanyl 50 µg [167] both studies reported good early analgesia. Side effects of intrathecal opioids include nausea, vomiting, pruritus, urinary retention and delayed respiratory depression. The lumbar epidural space is easy to locate making it an attractive technique in patients with, for example fixed spinal deformities. The combination of low-dose intrathecal morphine and a paravertebral block via a directly placed catheter has been suggested as an alternative to epidural analgesia post-thoracotomy [174].

Epidural Analgesia

Epidural injections via the sacral hiatus in dogs were described in 1901 [175]. The interspinous approach for epidural anaesthesia in clinical surgery was demonstrated in 1921 [176] and an article in 1933 by Dogliotti popularised epidural anaesthesia [177].

Post-thoracotomy thoracic epidural analgesia was introduced into clinical practice in the mid-1970s for high risk procedures [1, 2], by the mid-1980s it was being used by some for routine surgery [178] and by the 1990s it had become the mainstay of post-thoracotomy analgesia in many high volume Western units [3]. The widespread use of thoracic epidural for routine post-thoracotomy analgesia occurred because it provides effective, reliable post-thoracotomy analgesia, had been shown in a meta-analysis to reduce post-thoracotomy pulmonary complication [62] and was believed by many to improve the outcome after thoracic surgery.

Lumbar Epidural Analgesia

Lumbar epidural insertion is an easier and more familiar technique for most anaesthesiologists and also because of the absence of an underlying spinal cord lumbar epidurals are probably safer than thoracic epidurals. Lumbar epidural hydrophilic opioids are effective and were once used by a number of units to provide post-thoracotomy analgesia. Their widespread use declined when a meta-analysis showed that, unlike epidural local anaesthetics, epidural opioids did not reduce the incidence of post-operative pulmonary complications [62]. Late respiratory depression is also a potential problem with epidural hydrophilic opioids. Because of synergistic antinociceptive interactions, mixtures of local anaesthetics and opioids are now routinely used to provide post-thoracotomy analgesia [14]. Epidural mixtures of segmentally acting lipophilic opioids and local anaesthetics are best administered at the dermatomal level of the surgical incision. For thoracic procedures, this equates to a thoracic epidural. If the mixture is administered by a lumbar epidural away from the incision larger volumes are required, greater hemodynamic instability results and achieving good analgesia is more difficult. Lumbar epidurals are not now generally used for providing post-thoracotomy analgesia; however, in the occasional patient in whom attempts at placing a thoracic epidural are unsuccessful, a lumbar epidural may be appropriate. It is also a technique worth considering in the rare circumstance in which it is considered appropriate to insert an epidural in an anaesthetised patient.

Thoracic Epidural Analgesia

Technique of Insertion

After inserting a venous cannula and positioning the patient in either the lateral or sitting position, depending largely on operator preference, a wide area of the back is prepped with alcoholic chlorhexidine or an alternative antiseptic solution. At least two applications are recommended. The initial application should be with a sponge or similar material to abrade the superficial layers of the skin. Care should be taken to ensure that epidural drugs and equipment are not contaminated by the antiseptic used as all antiseptics are potentially neurotoxic. Similarly, the antiseptic solution used should be allowed to dry before commencing epidural insertion. The vertebral spinous processes are at their most oblique in the midthoracic region. At this level the tip of the spinous process is a landmark for the intervertebral space below the next vertebrae (see Fig. 46.12).

For the midline approach, a local anaesthetic wheal is raised over the appropriate vertebral interspace. A Tuohy needle is then inserted immediately above the palpable tip of the lower spinous process and advanced at the oblique cephalad angle determined by the obliquity of the spinous processes at this particular level. The angle of insertion may need adjustment if contact is made with a spinous process. For the paramedian approach, a local anaesthetic wheal is raised about 1 cm lateral to the palpable tip of the appropriate spinous process. A Tuohy needle is then inserted through this wheal perpendicular to all the planes. When contact is made with bone (lamina) the needle is withdrawn to the skin and angulated about 45° cephalad and 10° medial before being reinserted to the original depth[1].

FIG. 46.12. The thoracic vertebra. The steepest caudal inclination of the spinous processes is in the midthoracic region (this figure was published in Ramamurthy [277]. © Elsevier [1996]).

[1]Editors note: It has been my personal experience that the paramedian approach has greatly improved my success rate for mid-thoracic epidurals, T3–T8, deliberately walking the Tuohy needle medially and up the lamina.

The needle is then gradually advanced into the epidural space. If contact is again made with the lamina it may be necessary to walk the needle up the lamina to find the epidural space. After the tip of the Touhy needle has been in contact with bone it is advisable to ensure that the needle remains patent by gently re-inserting the trocar before re-advancing the needle.

It is known that during insertion epidural catheters do not follow a predictable course in the epidural space [179]. The optimal length of epidural catheter to leave in the epidural space is thus a balance between insufficient length resulting in catheter migration out of the space and excessive length resulting in technical failure because of malpositioning of the catheter tip. In a prospective analysis of post-operative epidural failure by computed tomography epidurolography during which 4 cm of epidural catheter was left in the epidural space 25% of the epidurals failed. The major cause of epidural failure was dislodgement of the epidural catheter out of the epidural space [180]. Four centimetre of catheter is probably insufficient for thoracic epidurals that are to remain in situ for a few days, 5–6 cm may be more appropriate [181]. Migration of the catheter out of the epidural space can be reduced by appropriate fixation with adhesive dressings, tunnelling or suturing. We recommend suturing of the catheter to the skin.

Epidural Solutions

High concentrations of unsupplemented thoracic epidural local anaesthetics can provide effective post-thoracotomy analgesia but the incidence of hypotension is high [182], while lower concentrations are less effective. Because the synergistic antinociceptive interactions of epidural local anaesthetics and opioids [183] enable the amount of each drug to be minimised reducing the incidence and severity of the associated side effects, mixtures of local anaesthetics and opioids are now routinely used to provide post-thoracotomy analgesia [14]. Although there is probably no epidural mixture that is optimal for all patients, a mixture of 5 μg mL^{-1} of fentanyl in 0.1% bupivacaine is close to the optimal [184–186]. The newer local anaesthetic agents (levobupivacaine and ropivacaine) are less toxic than bupivacaine and although relatively small amounts are administered epidurally, we now use 5 μg mL^{-1} of fentanyl in 0.1% levobupivacaine. The analgesic effects of epidural opioid and local anaesthetic mixtures are improved by epinephrine. Vasoconstriction of epidural vessels with reduced systemic uptake of epidural opioids is thought to be the major cause of this potentiation. The α-2 adrenergic action of epinephrine in the substantia gelatinosa may also contribute to the improved analgesia [187]. Potential cord ischemia as a result of excessive vasoconstrictive has limited the use of epidural epinephrine. Clonidine, another α-2 adrenergic agonist, when combined with epidural opioids, reduces opioid requirements and opioid-related side effects [188]. In a study using an optimisation model to find the best epidural combination of fentanyl, bupivacaine and clonidine to administer after laparotomy, the addition of clonidine did not significantly improve analgesia [184]. Epidural clonidine is not widely used to provide post-thoracotomy analgesia [14], although the addition of clonidine should be considered for patients who are particularly sensitive to the systemic effects of epidural opioids.

The extent of the sensory block after the administration of epidural anaesthetics varies considerably between individuals. A number of factors are known to affect the spread of the sensory block during thoracic epidural analgesia including the level at which the epidural is sited. For high thoracic epidurals the direction of spread is mainly caudal, for low thoracic epidurals the spread is mainly cranial and for midthoracic epidurals the spread is almost equally distributed [41, 189]. The total extent of the spread, however, is not significantly different at these three sites [41, 189]. While administering an epidural solution via a high thoracic epidural it may be appropriate to avoid neck flexion to further limit the potentially harmful cranial spread of the epidural solution [190]. Although widely believed and apparently logical, there is little evidence that the extent of thoracic epidural spread is related to the height of the patient [41]. Similarly, for adult patients weight does not appear to correlate with the extent of thoracic epidural spread [41]. There is, however, a positive correlation between the patient's age and the thoracic epidural spread, with elderly patients requiring about 40% less epidural solution [41, 42]. For younger patients, we usually administer a ~7 mL epidural bolus of a mixture containing 5 μg mL^{-1} of fentanyl in 0.1% levobupivacaine via a midthoracic catheter and then infuse the epidural solution at ~7 mL h^{-1}. For elderly patients, we reduce the bolus and infusion rate by about 40% (see Table 46.2 and Fig. 46.13)[2].

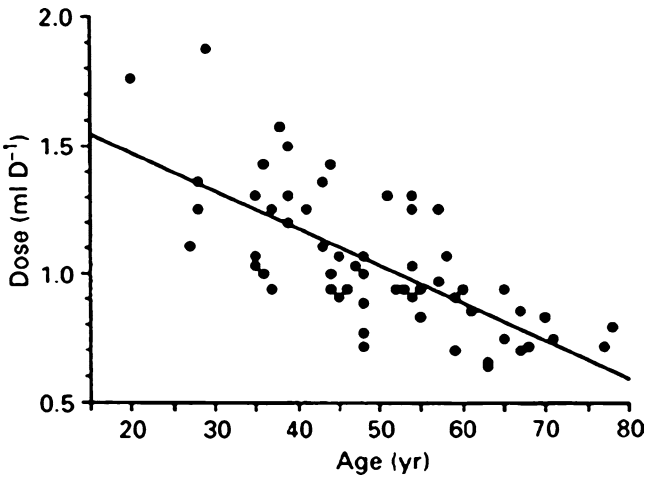


FIG. 46.13. Relationship between age and epidural dose requirements of 2% mepivacaine in thoracic epidural analgesia. *D* Dermatome (reproduced from Hirabayashi and Shimizu [42] by permission of Oxford University Press).

[2]Editors note: Several alternative protocols for thoracic epidural infusions are described in the addendum at the end of this chapter.

Benefits of Thoracic Epidural Analgesia

Thoracic epidurals provide excellent early post-thoracotomy analgesia and are widely regarded as the "gold standard" for post-thoracotomy pain relief.

Improved Post-operative Diaphragmatic Dysfunction

Prolonged diaphragmatic dysfunction has been shown to occur after thoracic [191] and upper abdominal [192] surgery. Diaphragmatic contractility is not impaired [193, 194] and the diaphragmatic dysfunction is thought to be secondary to reflex inhibition of the phrenic nerve as a result of stimulation of afferents in the viscera, diaphragm and chest wall [193]. Pain is not considered to be a major mediator of this dysfunction [195]. Thoracic epidural local anaesthetics have been shown to improve diaphragmatic function after upper abdominal surgery [196]. Epidural opioids are not effective [192]. Thoracic epidural local anaesthetics have not been shown to improve the impaired diaphragmatic segmental shortening after thoracotomy but other ventilatory parameters did improve. However, as epidural local anaesthetics can alter other respiratory muscle functions the improvement in diaphragmatic function may have been masked [191]. Thoracic epidural analgesia may directly affect functional residual capacity post-thoracotomy as an increase in functional residual capacity occurs in healthy humans receiving thoracic epidural analgesia [197].

Reduced Cardiovascular Complications

Cardiovascular complications contribute significantly to post-thoracotomy morbidity and mortality. Thoracic epidural local anaesthetics can block the sympathetic nerve fibres to the heart (T1–T5) and have been used to treat refractory angina [198, 199]. Thoracic epidural analgesia can also dilate constricted coronary arteries and improve the hemodynamic stability of patients undergoing thoracic surgery. These changes have the potential to reduce myocardial ischaemia. A meta-analysis of patients undergoing various surgeries has confirmed this potential and shows that epidural analgesia reduces post-operative myocardial infarctions by 40%; thoracic epidural analgesia is superior to lumbar epidural analgesia in this respect [200]. There is some evidence that thoracic epidural local anaesthetics reduce the incidence of supraventricular arrhythmias [201], which occur in 20–30% of post-thoracotomy patients [202, 203] and are associated with an increased mortality [204, 205].

Thoracic Epidurals and Outcome

The mortality from lung cancer surgery has decreased over the last few decades and this reduction in post-thoracotomy mortality has been attributed, in part, to improvements in post-operative analgesia. There are a number of possible mechanisms whereby thoracic epidural analgesia may reduce respiratory complications post-thoracotomy. These include better preservation of functional residual capacity, improved mucociliary clearance, reduction of inhibitory effects on the diaphragm, less pain, nausea and sedation and better collaboration with physiotherapy. Although transferable evidence and early analysis found that when compared with systemic analgesia, thoracic epidural analgesia reduced post-operative pulmonary complications [62], later quantitative analyses have not shown this reduction [10]. Similarly, although thoracic epidurals may decrease peri-operative myocardial infarctions [200] and reduce the incidence of thrombo-embolic events [206, 207] there are no prospective studies showing thoracic epidurals improve survival after thoracotomy. A meta-analysis of randomised controlled studies did show reduced mortality with neuroaxial blocks after surgery but much of this effect was after orthopaedic surgery [208]. In contrast, a large prospective randomised study of patients undergoing major abdominal surgery did not show epidural analgesia to be associated with reduced mortality [209]. A large prospective study is required to determine if post-thoracotomy outcome is improved with thoracic epidural analgesia.

Limitations and Adverse Effects

The reported rates of epidural failure vary. Although successful catheter placement rates of 99% and subsequent technical failure rates of <1% have been reported [210], some audits have reported a 30–50% failure rate [211] and a recent meta-analysis reported a 15% thoracic epidural failure rate [11]. Thoracic epidurals are considered technically more difficult to insert than lumbar epidurals; however, the dural perforation rate has been found to be lower during thoracic epidural insertion (0.9%) than during lumbar epidural insertion (3.4%) [210]. Respiratory depression is a concern with epidural opioids particularly hydrophilic opioids. The incidence is related to the type and dose of the epidural opioids used. A Swedish study also found that age >70 year and the administration of additional opioids by other routes were risk factors for the development of respiratory depression [212]. However, the reported incidence of respiratory depression with fentanyl local anaesthetic epidurals of 0.3% [213] is no higher than the incidence of respiratory depression when opioids are administered by other routes. Drug errors whereby the wrong drug is administered epidurally have been reported [214] but fortunately are rare and should be reduced further by using dedicated epidural delivery systems. The reported incidence of serious complications has varied although an estimate of 0.0007% is often quoted. The Third National Audit Project, the largest prospective study of complications after central neuraxial blocks, has helped clarify the incidence of serious complications associated with epidurals [4, 5]. This confirmed that overall (peri-operative, obstetric, paediatric and chronic pain) central nerve blocks were associated with a very low (0.007%) incidence of major complications. The incidence of major complication after epidurals inserted peri-operatively was, however, much higher at 0.02%. The most frequent complications were epidural haematomas [5]. This incidence of major complications after peri-operative epidurals is almost the same as that incidence reported in an earlier Swedish study [215].

Neuroaxial Block and Coagulation

Due to the rarity of spinal epidural hematomata case reports, expert opinion, not scientific evidence from controlled trials, provides the mainstay of recommendations for epidural analgesia in patients receiving antithrombotic medications. This is particularly true for thromboprophylaxis [216]. The risk of an epidural inserted for post-thoracotomy analgesia resulting in a permanent injury or death is approximately 0.02%. Epidural haematomas account for most of this morbidity [4, 5]. Anticoagulants and antiplatelet agents can further increase the risk of vertebral canal haematoma [217, 218] and may increase the risk of epidural abscesses by causing small haematomas that become secondarily infected. All patients receiving thoracic epidural analgesia and patients who have undergone unsuccessful attempts at epidural catheter placement should be monitored regularly for symptoms and signs of vertebral canal haematoma, specifically back pain, motor or sensory changes and urinary retention (if not catheterised). Of these, motor block is the most reliable sign and most sensitive prognostic indicator [219]. Vertebral canal haematoma occurring in the peri-operative period have a poor outcome.

Oral Anticoagulants (Warfarin)

When thoracic epidural analgesia is planned warfarin should be discontinued at least 4–5 days pre-operatively. The INR should be within normal limits prior to placing the epidural catheter to ensure adequate levels of active vitamin K-dependent clotting factors. Haemostasis may not be adequate even with an INR of 1.3 [6]. Warfarin therapy should not be reinstituted until after removal of the epidural catheter and the INR should be <1.5 prior to catheter removal.

Antiplatelet Medications

There is considerable variability in patient responses to antiplatelet agents. The increased risk in individual patients may therefore be difficult to quantify, although female sex, advanced age and a history of easily bruising can signify an increased risk. The role of near-patient testing of platelet function prior to neuraxial block needs to be established.

NSAIDs (Including Aspirin)

NSAIDs appear not to increase the risk of vertebral canal haematoma in patients undergoing neuroaxial blockade [6, 220, 221]. Concurrent administration of other haemostasis altering medications does, however, appear to increase the risk of bleeding [6], especially in the case of aspirin. This includes heparin for post-operative thromboprophylaxis [216, 218]. Thus, if feasible, aspirin should be discontinued 5–7 days prior to surgery if central neuraxial blockade and heparin-based DVT prophylaxis is planned.

Thienopyridine Derivatives

These include clopidogrel and ticlopidine. They are potent antiplatelet agents causing irreversible inhibition of ADP-induced platelet aggregation and platelet–fibrinogen binding inhibition. Clopidogrel should be discontinued at least 7 days and ticlopidine at least 10–14 days prior to neuraxial blockade [6].

Herbal (Alternative) Medication [6, 216]

Up to 50% of surgical patients may be taking herbal medications pre-operatively although many do not volunteer this information. Although herbal drugs by themselves probably pose no significant added risk, Garlic, Ginseng and Gingko have raised concern because they are associated with thrombocytopenia, inhibition of platelet aggregation and interaction with vitamin K antagonists. There may be a small increased risk of an epidural haematoma if patients receive heparin for thromboembolism prophylaxis. It is probably wise to actively seek a history of such herbal therapy usage and discontinue it 7 days pre-operatively.

Coronary Stents

An increasing number of patients with coronary artery stents in situ and receiving antiplatelet drugs are presenting for thoracic surgery. After insertion patients receiving bare metal stents require aspirin and clopidogrel for at least 4 weeks. Patients receiving drug eluting stents require aspirin and clopidogrel for at least 12 months. All patients with stents in situ require aspirin for life [7, 9, 222]. Dual-antiplatelet therapy is a contraindication to epidural analgesia [6]. Although discontinuing clopidogrel ≥7 days pre-operatively while continuing aspirin may make thoracic epidural feasible, the premature discontinuation of one antiplatelet agent markedly increases the risk of acute peri-operative stent thrombosis with significant cardiac morbidity and mortality [7–9]. Aspirin therapy should rarely be interrupted [9]. The planned duration of post-operative epidural analgesia is also relevant as antiplatelet therapy should be recommenced as soon as possible post-procedure as delays may expose the patient to an unacceptable risk of stent thrombosis [7].

Thromboprophylaxis

Subcutaneous unfractionated heparin is effective in reducing the incidence of thromboembolic complications [6, 223]. As there have been only five case reports of vertebral canal haematomata associated with neuraxial blockade in patients receiving subcutaneous unfractionated heparin published in the literature [224–226] subcutaneous heparin in patients with thoracic epidurals in situ appears safe [227]. If subcutaneous heparin is continued for greater than 4–5 days a platelet count is recommended prior to removal of the epidural catheter as heparin-induced thrombocytopenia may occur. Low molecular weight heparins have different biochemical and pharmacological properties to unfractionated heparin including anti-Xa activity [6]. The half life of anticoagulant activity following the administration of a dose of subcutaneous low molecular weight heparin is considerably longer than that following a subcutaneous dose of unfractionated heparin, allowing once daily dosage. In the late 1990s, there were reports of more than 40 cases of vertebral canal hematomata in patients following neuraxial blockade in the United States. This may have been the result of the North American guidelines recommending twice daily dosage, meaning there was effectively no "safe" time in which to perform a block or remove an epidural catheter. Similar clusters of cases of hematomata were not reported in Europe despite extensive experience of regional blockade

concurrent with low molecular weight heparin thromboprophylaxis [228, 229]. This is thought to represent the once daily dosage employed in Europe. However, despite this neuraxial blockade in the presence of low molecular weight heparin thromboprophylaxis is more risky than with unfractionated heparin, especially for epidural catheter techniques [6].

Urinary Retention

Urinary retention is a well-known complication of epidural opioids use [230]. The mechanisms for this include inhibition of the sacral parasympathetic outflow and inhibition of the pontine micturition centre [231]. Epidural morphine-mediated reduction in detrusor muscle function is antagonised by naloxone [232] and in post-hysterectomy patients naloxone can reverse bladder dysfunction without reversing epidural morphine analgesia [233]. However, when given to post-thoracotomy patients receiving thoracic fentanyl bupivacaine epidural analgesia, naloxone reversed the analgesic effects of the epidural without reducing the need for urinary catheterisation [234] and is not recommended for this purpose.

Gastric Emptying

The excellent early analgesia provided by thoracic epidural analgesia enables most patients to resume their normal diet and oral medications a few hours post-thoracotomy. The rate-limiting step for the absorption of most orally administered drugs is gastric emptying. Gastric emptying is variably affected by anaesthesia and surgery [235–237]. Epidural opioids can result in gastric hypomobility. Branches of the T6–T10 sympathetic nerves innervate the stomach [238] and sympathetic blockade of these nerves could hasten gastric emptying. Gastric emptying has been shown to be normal in patients receiving bupivacaine epidural analgesia post-cholecystectomy [237]. For post-thoracotomy patients receiving a fentanyl bupivacaine, thoracic epidural gastric emptying is delayed for >48 h [239]. This delayed gastric emptying may lead to reflux or regurgitation and altered effects of orally administered drugs.

Hypotension

Hypotension is a common clinical occurrence during thoracic epidural analgesia. It is important to appreciate the differences between hypotension due to a lumbar vs. mid-thoracic epidural sympathetic blockade. With lumbar neuraxial blockade, hypotension is primarily due to systemic vasodilation, decreasing cardiac preload and afterload. The hypotension due to thoracic epidural blockade occurs for these two previous reasons and also due to blockade of the cardiac sympathetic supply, T2–T4, which interferes with the heart's ability to increase contractility. Unlike treatment of hypotension during lumbar blockade, hypotension during thoracic epidural blockade will have a limited response to increases of preload and afterload and therefore requires treatment with a β-adrenergic or mixed agonist (e.g. ephedrine, dopamine, etc.) to increase cardiac contractility and restore cardiac output [240].

Shoulder Pain

Ipsilateral shoulder pain is common in patients receiving effective thoracic epidural analgesia and occurs occasionally in patients receiving paravertebral blocks, but is rare in patients not receiving nerve blocks for post-thoracotomy analgesia. The reported incidence of ipsilateral shoulder pain in patients receiving thoracic epidural analgesia varies from 42 to 86% [18, 19, 109, 142, 241]. This shoulder pain is often described by patients as an ache, usually of moderate to severe intensity, and lasts for a few days. Early explanations of this shoulder pain were that it was related to the transection of a major bronchus although no mechanism was suggested [18]. Other early explanations included stretching of the brachial plexus or the shoulder joint as a result of the intra-operative positioning and distraction of the posterior thoracic ligaments by surgical retractors [17]. Recent studies have helped explain the pathogenesis of this pain. A double-blind study of patients who had developed ipsilateral post-thoracotomy shoulder pain in which patients were given either bupivacaine or saline to block the suprascapular nerve found that blocking the suprascapular nerve did not affect the incidence of pain [241]. This makes intra-operative shoulder distraction an unlikely cause of ipsilateral post-thoracotomy shoulder pain. A placebo-controlled study of the administration of bupivacaine through the basal drain found that bupivacaine was not effective in reducing ipsilateral post-thoracotomy shoulder pain [142]. Irritation of the diaphragmatic pleura by a basal chest drain is therefore unlikely to be a significant cause of ipsilateral post-thoracotomy shoulder pain. A placebo-controlled study in which the periphrenic fat pad, at the level of the diaphragm, was infiltrated with either lidocaine or saline intraoperatively reduced the early incidence of ipsilateral post-thoracotomy shoulder pain from 85 to 33% [19] (see Fig. 46.14).

This marked reduction in the incidence of ipsilateral post-thoracotomy shoulder pain with phrenic nerve infiltration was confirmed in a later study [242]. The phrenic nerve must therefore be importantly involved in the pathogenesis of ipsilateral

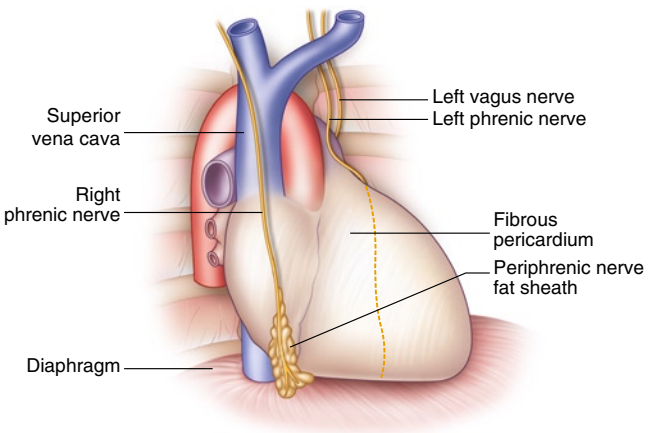


FIG. 46.14. Diagram to illustrate the site of the periphrenic nerve fat sheath for phrenic nerve blocks (modified with permission from Gosling et al. [278] and Scawn et al. [19]).

post-thoracotomy shoulder pain. The phrenic nerve supplies sensory branches to the mediastinal pleura, the fibrous pericardium, the parietal layer of the serous pericardium and the pleura related to the central part of the diaphragm. In most patients, the likely explanation of ipsilateral post-thoracotomy shoulder pain is irritation of the pericardium, mediastinal and diaphragmatic pleural surfaces resulting in pain referred to the shoulder via the phrenic nerve. In a few patients with ipsilateral post-thoracotomy shoulder pain and an apical chest drain extending to the apex of the chest cavity, withdrawal of the chest drain by a few centimetres relieves the pain. This implies that irritation of the apical pleura by the chest drain is another cause of ipsilateral post-thoracotomy shoulder pain.

Recent studies have helped guide the treatment of ipsilateral post-thoracotomy shoulder pain. The pain is resistant to epidural boluses [76] and intravenous opioids [19]. Pre-operative gabapentin [109] is similarly ineffective. Effective treatment options for ipsilateral post-thoracotomy shoulder pain include acetaminophen [93], non-steroidal anti-inflammatory agents [18, 76], direct intra-operative phrenic nerve blocks [19, 242] and indirect post-operative phrenic nerve blocks [243, 244]. Rectal acetaminophen is safe and moderately effective [93] although personal experience suggests intravenous acetaminophen to be more effective. The use of acetaminophen orally, rectally or intravenously to treat ipsilateral post-thoracotomy shoulder pain is recommended. Non-steroidal anti-inflammatory agents are effective in controlling ipsilateral post-thoracotomy shoulder pain [18, 76] and personal experience suggests that they are more effective than acetaminophen. The well-known side effects of NSAIDs are, however, a particular concern in the often old and debilitated patients who have undergone thoracic surgery and the risks should be assessed before their use. Intra-operative phrenic nerve blocks are effective. The short duration of effect with lidocaine [19] can be extended by the use of ropivacaine [242] but patient selection is important as the resultant unilateral diaphragmatic paresis can further impair ventilation. Phrenic nerve blocks should be considered for patients in whom post-operative pulmonary function is not a concern and for patients undergoing a pneumonectomy. In post-pneumonectomy patients, the unilateral loss of diaphragmatic function has limited effects on ventilation and may have an additional benefit of helping to reduce the pneumonectomy space. Post-operative interscalene brachial plexus blocks have been shown to be effective in treating ipsilateral post-thoracotomy shoulder pain in case reports [243] and in a prospective study [244]. The phrenic nerve block that is a side effect of interscalene brachial plexus block [245] almost certainly explains the blocks effectiveness. Because of the potential complications associated with this block we recommend that interscalene brachial plexus blocks be considered only in patients with severe ipsilateral post-thoracotomy shoulder pain and adequate pulmonary reserve. Although a stellate ganglion block may be effective in treating ipsilateral post-thoracotomy shoulder pain [246], its use for this purpose is not recommended.

Techniques for Specific Procedures

Sternotomy

A sternotomy can be used to provide access for a range of surgical procedures including the resection of anterior mediastinal tumours. At closure the divided sternum is usually internally fixed with wire. This fixation restricts bone movement and limits pain. Adequate post-sternotomy analgesia can usually be achieved with a morphine IV-PCA system supplemented when appropriate by non-opioid analgesics. Local anaesthetic wound infiltration can reduce opioid consumption [247] and should be considered. Continuous wound infiltration via deep and/or subcutaneous catheters may be more effective but evidence of effectiveness is limited, with some studies showing no benefit [248]. Thoracic epidurals can provide very effective post-sternotomy analgesia. The catheter should be sited at a higher level (T3/T4) than for a thoracotomy (T6/T7) and any parasthesia of the medial surface of the arms detected early, to enable a timely reduction in the epidural infusion rate to limit the risk of bilateral phrenic nerve (C4–C5) blocks. Thoracic epidural analgesia should be considered for patients with poor lung function undergoing bilateral pulmonary procedures via a sternotomy (e.g. volume reduction surgery). A parasternal local anaesthetic block can reduce opioid requirements [249] and should be considered in patients with poor lung function in whom epidural anaesthesia is contraindicated.

Video-Assisted Surgery

The limited incision may limit post-operative pain. The appropriate analgesia depends in part on the nature of the surgery undertaken. Thoracic epidural analgesia is usually provided for patients undergoing VAT lung volume reduction surgery and may be advantageous in patients undergoing minimally invasive oesophagectomies [250]. Paravertebral blocks and/or an IV-PCA system may be appropriate for patients undergoing VAT lung resections. Minimal analgesia may be required after VAT pleural biopsies or sympathectomies.

Open Thoracotomy

A large number of pain management techniques have been described for open thoracotomy patients. These have included the administration of local anaesthetics, opioids and other drugs to provide intercostal nerve blocks [128–130], interpleural blocks [136–139], paravertebral blocks [162, 251, 252], lumbar epidural analgesia [253–255], thoracic epidural analgesia [1, 2, 178, 185, 186], intrathecal analgesia [166–172] and systemic analgesia [10]. In addition, the non-pharmacological techniques of cryoanalgesia [123, 124] and TENS [116–122] have been used. Good post-thoracotomy pain control is difficult to achieve without regional anaesthesia (or multiple nerve blocks) and it is recommended that a regional anaesthetic technique be used alone, or in combination with

systemic analgesics, to provide post-thoracotomy analgesia. As apart from paravertebral blocks all other regional analgesic techniques are inferior to thoracic epidural analgesia [10], the choice of regional anaesthetic technique is usually between thoracic epidural analgesia and a paravertebral block.

Thoracic epidurals usually provide post-thoracotomy analgesia with an epidural mixture of opioids and local anaesthetics; patients usually receive no systemic analgesics apart from perhaps acetaminophen or NSAIDs for shoulder pain. In contrast, paravertebral blocks are usually supplemented with systemic morphine, NSAIDs and other systemic analgesics for at least the early post-operative period. These differences are important in the interpretation of studies that have compared thoracic epidural analgesia and paravertebral blocks. A meta-analysis published in 2006 included 10 trials with 520 enrolled patients [11]. In six of the trials, the epidural group received higher concentrations of epidural local anaesthetics than generally used [14] or recommended. It is well known that the incidence of post-operative hypotension is increased when higher concentrations of epidural local anaesthetics are used. Similarly, in only four of the trials were epidural local anaesthetics supplemented with opioids used as is recommended and usual practice [14]. Notwithstanding these limitations, it was concluded that the two techniques provided comparable analgesia and that pulmonary complications were lower in the paravertebral group [11]. Similarly, a 2008 review of regional techniques for post-thoracotomy analgesia found that a continuous thoracic epidural infusion of local anaesthetics and opioids provided the most consistently effective analgesia [10]. However, when compared to systematic analgesia, thoracic paravertebral blocks, but not thoracic epidural analgesia, reduced the incidence of pulmonary complications [10]. In practice both techniques have advantages in particular patients and the acquisition of expertise in both techniques is recommended. For patients with borderline predicted post-operative lung function, good early analgesia and the ability to co-operate with lung recruitment manoeuvres immediately post-operatively may be critical. Correctly sited thoracic epidurals provide reliable good early analgesia with minimal sedation and their use in this scenario is recommended. A retrospective analysis of one institute's data showed that a pre-operative FEV_1 of less than 60% predicted was an independent risk factor for the development of post-thoracotomy pulmonary complications and mortality. The use of thoracic epidural analgesia was associated with reduced pulmonary complications and a reduced mortality in patients with an $FEV_1 < 60\%$, although no patients were reported to have received a paravertebral block [256] (see Fig. 46.15). A prospective 1-year observational study of pneumonectomies in the United Kingdom found epidural analgesia to be a significant associate of poor outcome [257].

For patients with good pulmonary function undergoing limited lung resection, early analgesia may be less critical and paravertebral analgesia may enable earlier mobilisation and shorten hospital stays. For most patients, the decision is less clear cut and consideration of the relative risks and benefits of the two techniques should be made for the particular patient (see Table 46.3). For patients for whom neither thoracic epidural or paravertebral blocks is appropriate consideration should be given to the use of intercostal nerve blocks or pre-operative intrathecal opioids.

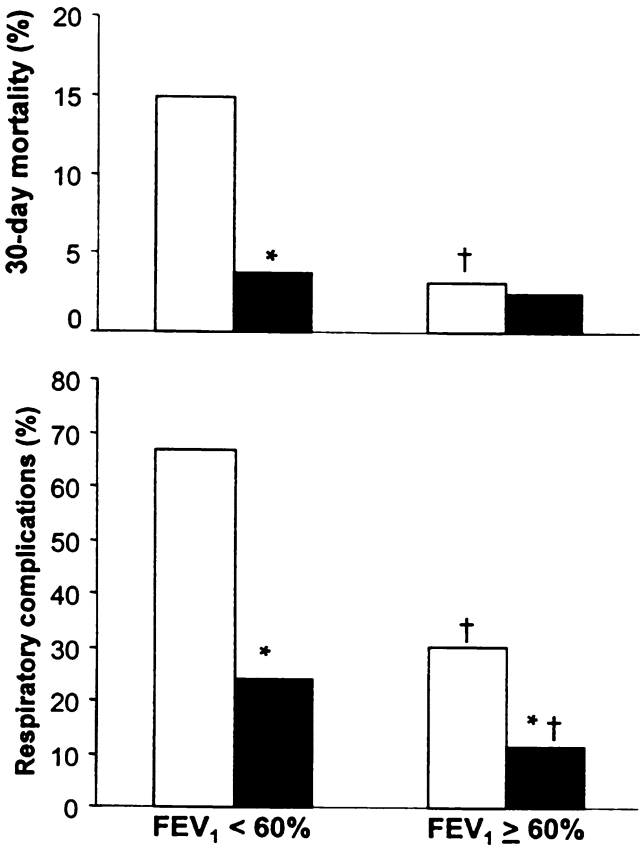


FIG. 46.15. Thirty-day mortality rate (*top*) and incidence of respiratory complications (*bottom*) according to pre-operative FEV_1 (<60% or ≥60%) and type of analgesic regimen: without thoracic epidural analgesia (*white bars*) or with thoracic epidural analgesia (*black bars*). $*p<0.05$, compared with group without thoracic epidural analgesia; $^{\dagger}p<0.05$, compared with group $FEV_1 \geq 60\%$ (*FEV_1* forced expiratory volume in 1 s) (this figure was published in Licker et al. [256]. © Elsevier [2006]).

TABLE 46.3. Factors influencing choice of paravertebral block or thoracic epidural.

Favours thoracic epidural	Favours paravertebral block
Poor PFTs	Good PFTs
Extensive lung resection	Limited lung resection
Chest wall involvement	Sepsis
Non-steroidal anti-inflammatory drugs (NSAIDs) contraindicated	Impaired coagulation
Patient preference	Patient preference
	Fixed spinal deformity
	Anaesthetised patient

PFTs Pulmonary function tests

Oesophageal Surgery

Post-operative pain can be very severe after open oesophageal surgery and thoracic epidural analgesia is usually used to provide post-operative analgesia for these patients. For patients undergoing a minimally invasive oesophagectomy, the combination of an IV-PCA system, a paravertebral block and non-opioid analgesics is frequently used. Recent work, however, found an increased mortality in patients undergoing a minimally invasive oesophagectomy without a thoracic epidural [250] and a thoracic epidural should be considered for all patients scheduled to undergo an oesophagectomy. Post-oesophagectomy thoracic epidural analgesia probably has benefits in addition to providing good analgesia. In non-randomised studies comparing systemic opioids with epidural analgesia after open oesophageal surgery, patients receiving epidural analgesia had fewer respiratory complications [258], spent less time in intensive care [258, 259] and had a lower mortality [258, 260, 261]. In 1994, Watson and Allen [261] stated that in their experience "the routine use of thoracic epidural analgesia has been the most significant advance in the management of patients with oesophageal cancer during the past 15 years". Similarly, Law et al. [262] attributed their low post-oesophagectomy complication rate to thoracic epidural analgesia and said "Perhaps the most important advance in peri-operative care in oesophagectomy in the 1990s was the use of epidural analgesia, which was shown to reduce complications and death rate". Thoracic epidurals may decrease the incidence of anastomotic leakage post-oesophagectomy [263]. Ischemia at the anastomotic end of the newly formed gastric tube is a major cause of anastomotic leaks post-oesophagectomy [264]. A relationship between low Doppler determined blood flow at the anastomotic site and subsequent anastomotic leakage has been shown [265]. Although intra-operative epidural boluses can cause hypotension and reduced blood flow to the anastomotic end of the gastric tube [266], a study using continuous post-operative thoracic epidurals found epidurals to be associated with minimal hypotension and an increased distal conduit blood flow [267]. We recommend that "anesthesiologists should be cautious in accepting intra-operative hypotension secondary to epidural administration in patients undergoing esophagectomy" [266]. For patients undergoing open oesophageal surgery in whom epidural analgesia is inappropriate or contraindicated consideration should be given to the use of a continuous paravertebral block as they have been reported to provide reasonable analgesia when supplemented by systemic analgesics [268].

Opioid Tolerant Patients

Opioid tolerant patients presenting for thoracic surgery include patients with malignant diseases receiving opioids for pain, a rapidly increasing group of patients with non-malignant disease receiving opioids chronically for pain management, opioid-dependent substance abusers and former addicts on long-term maintenance programmes. The principles of treatment are similar for all groups but opioid substance abusers may present additional challenges due to their psychological problems, dependency on other substances (e.g. alcohol) and concomitant infectious diseases (e.g. tuberculosis, human immunodeficiency virus) which may affect the delivery of anaesthesia.

Achieving good post-operative analgesia in patients who are chronically receiving opioids is frequently difficult and these patients may experience more post-operative pain. Patients should when practical be involved in the plans for their post-operative pain management. Abrupt cessation of opioids can result in an acute opioid withdrawal syndrome and should be avoided. Naltrexone, a long acting opioid antagonist used to help prevent relapse in detoxified former opioid dependent patients, should be discontinued a few days before surgery. The route and usual daily dose of opioids should be established, and for patients scheduled for major surgery and an equivalent intravenous dose of morphine estimated. Unfortunately, variability in the pharmacokinetics, pharmacodynamics, route of administration and daily opioid consumption make estimating a morphine equivalent dose difficult. For opioid naïve patients, receiving an IV-PCA for post-thoracotomy analgesia, a background opioid infusion is usually not appropriate. Opioid-dependent patients however should, in addition to any demand opioids, receive at least 50% of their usual dose of opioid orally, or if this is not appropriate, as a background infusion throughout the peri-operative period. Most patients undergoing open thoracic surgery benefit from the addition of a regional anaesthetic technique and/or the addition of adjunctive pharmacologic agents to their opioids. Thoracic epidurals can provide excellent post-thoracotomy analgesia in opioid tolerant patients and their use is recommended. The use of a lipophilic opioid local anaesthetic mixture is recommended. Lipophilic opioids local anaesthetic mixtures have been shown to provide pain control that is superior to morphine local anaesthetic mixtures in opioids tolerant patients perhaps because analgesic effects are exerted at lower receptor occupancy [269, 270]. An alternative for patients scheduled to receive significant amounts of opioids by other routes is the use of a plain local anaesthetic epidural solution. Where thoracic epidural use is inappropriate a surgically placed catheter and paravertebral infusion is recommended. Non-opioid adjuvant analgesic agents should also be considered. The use of NSAIDs or COX-2 inhibitors is particularly appropriate for opioid tolerant patients and their use is recommended although there are few studies evaluating their use in opioid-dependent patients.

For a few patients, parental opioids may be the most appropriate means of providing post-operative analgesia. Despite earlier concerns of increasing addiction and manipulative behaviour, the use of intravenous IV-PCA systems to

control pain in substance abusers is now generally considered acceptable, if this system is used appropriately. Predicting the postoperative opioid requirement for opioid-dependent patients is difficult. Opioid tolerant patients are more likely to become sedated than opioid naïve patients despite having higher pain scores [271]. Swenson et al noted that during drug administration there is initially a disparity between the plasma concentration and the concentration of the drug at its site of action (effect site concentration). They describe a method of determining the effect site concentration of fentanyl at the threshold of respiratory depression in individual patients using simulation software and a fentanyl infusion. After determining the effect site concentration of fentanyl at the threshold for respiratory depression an hourly fentanyl administration rate that will result in 30% of this effect site concentration is calculated. Utilising an intravenous PCA system half of this calculated fentanyl dose can be administered as a background infusion while the remaining 50% is programmed for demand administration as boluses with a 15-min lockout period. They recommend that the regimen be reviewed at 4 hourly intervals and adjustments made based on the number of demand boluses administered, the level of conscious and the respiratory rate [272]. Methadone, a NMDA receptor antagonist which can activate α adrenergic receptors and a different range of μ receptors subtypes to morphine, is regarded as the intravenous PCA opioid of choice for opioid-dependent patients by some authors [273]. Consideration should be given to using a methadone IV-PCA system in opioid-dependent patients whose post-operative pain is refractory to large doses of systemic morphine. The administration of a low dose ketamine infusion should be considered particularly in patients for whom regional anaesthetic techniques are not planned. The literature suggests that for opioids tolerant patients an intra-operative bolus of ketamine (~0.25 mg kg^{-1}) should be followed by an intravenous infusion (~2 μg kg^{-1} min^{-1}) continued for a few days [274]. Although adding ketamine to morphine delivered via an IV-PCA has been described [101] this is not recommended in opioids tolerant patients because the large and unpredictable opioids requirements may result in the administration of excessive doses of ketamine with the associated psychotropic side effects [274].

Conclusion

Pain control after surgery is central to the anaesthetic management of patients undergoing thoracic surgery. The provision of good post-operative analgesia is of itself important and is regarded by some as the core business of anaesthesia and a fundamental human right [275]. Effective analgesia can reduce pulmonary complications and mortality [256]. It is unlikely that a single technique will optimally fulfil these objectives for all patients. Analgesia should be tailored to the specific patient undergoing a specific procedure and aim to minimise mortality, patient suffering, pulmonary complications and other morbidity. Experience with a wide range of analgesic techniques is helpful as it enables the implementation of an appropriate technique. For open thoracotomies most patients are best managed by a combination of regional analgesia and opioids, sometimes supplemented with non-opioid analgesics. There is no role for interpleural blocks or cryoanalgesia in adults. Lumbar epidural analgesia, intrathecal opioids or intercostal nerve blocks should usually be considered only if neither thoracic epidural analgesia or paravertebral blocks are possible. At present the dilemma for thoracic anaesthetists and their patients scheduled to undergo a thoracotomy is the choice between thoracic epidural analgesia and paravertebral block. It has been well established that thoracic epidurals produce excellent post-thoracotomy analgesia. There is also evidence that thoracic epidural analgesia reduces post-thoracotomy pulmonary complication [256] although these advantages have not been shown in recent analyses particularly when thoracic epidurals are compared with paravertebrals [10, 11]. Thoracic epidurals are associated with a risk of permanent injury and this risk is orders of magnitude greater than the risks associated with lumbar epidural administered in parturients [5]. The most frequent disabling complications are epidural haematomas [5]. An increasing number of patients presenting for thoracic surgery are receiving drugs that affect coagulation, not all of which are prescribed. Current anticoagulant and antiplatelet medication increases the risk of epidural by an unquantified amount. Impaired coagulation is less of a contraindication to thoracic paravertebrals, particularly when they are inserted under direct vision. Serious complications are rare with paravertebrals. Recent meta-analysis and systemic analysis have suggested that paravertebrals are more effective at reducing pulmonary complications than thoracic epidurals [10, 11]. However, only a limited number of patients have been enrolled in studies comparing paravertebrals with thoracic epidural analgesia and many received suboptimal epidural solutions. It is anticipated that in the future additional data on the relative benefits of opioid/local anaesthetic thoracic epidural vs. paravertebral with systemic opioids will aid the difficult decision on epidural insertion for high risk patients who are also at increased risk of epidural related complications. In the future, the development of clinically useable ultra-long acting local anaesthetics might enable significant further advances to be made in the provision of post-thoracotomy analgesia.

Addendum

Editors note: For the reader's further information, Figs. 46.16, and 46.17 are protocols for Patient Controlled Epidural Analgesia after thoracic or upper abdominal surgery from the Toronto General Hospital.

FIG. 46.16. (**a**, **b**) Standard anaesthesiologist order sheets for thoracic epidural analgesia infusions with patient-controlled boluses p.r.n., following thoracic or upper abdominal surgery (images courtesy of the Toronto General Hospital).

a

While on PCEA device, the patient is to receive No further supplemental Opioids or other CNS depressants unless approved by the Anaesthesia/Acute Pain Service.

Only the patient should press the PCEA delivery pendant unless otherwise directed by the APS.
(Check ☑ appropriate box(es) and complete orders as required)

1. MONITORING:
Patient Monitoring as per PCEA Flowsheet Form No. 2444

2. MEDICATIONS: Common PCEA Orders

❒ Single dose opioid injection:
❒ Epidural ❒ Spinal/Intrathecal
Operating Room Dose: Drug_____mg Time _____hrs

❒ **T 4 – 6 Level**: **Bupivacaine 0.1% and Hydromorphone** 0.015 mg/mL in 250 mL normal Saline; Epidural Rate 4 mL/h; Bolus dose 2 mL; Lockout period 20 min; 4 h limit 40 mL

❒ **T 7-11 Level**: **Bupivacaine 0.1% and Hydromorphone** 0.015 mg/mL in 250 mL normal Saline; Epidural Rate 5 mL/h; Bolus dose 3 mL; Lockout period 20 min; 4 h limit 50 mL

❒ **T 12 – L4 Level**: **Bupivacaine 0.1% and Hydromorphone** 0.015 mg/mL in 250 mL normal Saline; Epidural Rate 8 mL/h; Bolus dose 3 mL; Lockout period 20 min; 4 h limit 60 mL

❒ **T 4 – 6 Level**: **Ropivacaine 0.2%** in 200 mL Normal Saline; Epidural Rate 4 mL/ h; Bolus dose 2 mL; Lockout period 20 min; 4 h limit 40 mL

❒ **T 7-11 Level**: **Ropivacaine 0.2%** in 200 mL Normal Saline; Epidural Rate 5 mL/ h; Bolus dose 3 mL; Lockout period 20 min; 4 h limit 50 mL

❒ **T 12 – L4 Level**: **Ropivacaine 0.2%** in 200 mL Normal Saline; Epidural Rate 8 mL/ h; Bolus dose 3 mL; Lockout period 20 min; 4 h limit 60 mL

Associated Medications
❒ DimenhyDRINATE (Gravol®) 25-50 mg IV-int / IM q 3 h PRN for nausea
❒ Granisetron (Kytril®) 1 mg IV-int q 24 h x 2 doses PRN for nausea
❒ DiphenHYDRAMINE (Benadryl®) 25-50 mg IV-int q 3 h PRN for pruritis

b

(Check ☑ appropriate box(es) and complete orders as required)

Other Epidural Solutions
❒ Bupivacaine 0.1% and Hydromorphone 0.015 mg in 250 mL normal Saline; Epidural Rate ___ mL/ h; Bolus dose ___mL; Lockout period __ min; 4 h limit ____mL
❒ Bupivacaine 0.1% and Fentanyl 4 mcg/mL in 250 mL normal Saline; Epidural Rate ___ mL/h; Bolus dose ___mL; Lockut period ___min; 4 h limit ___mL
❒ Ropivacaine 0.2% in 200 mL Normal Saline; Epidural Rate ___mL/h; Bolus dose ___mL; Lockout period 20 min; 4 h limit ____mL

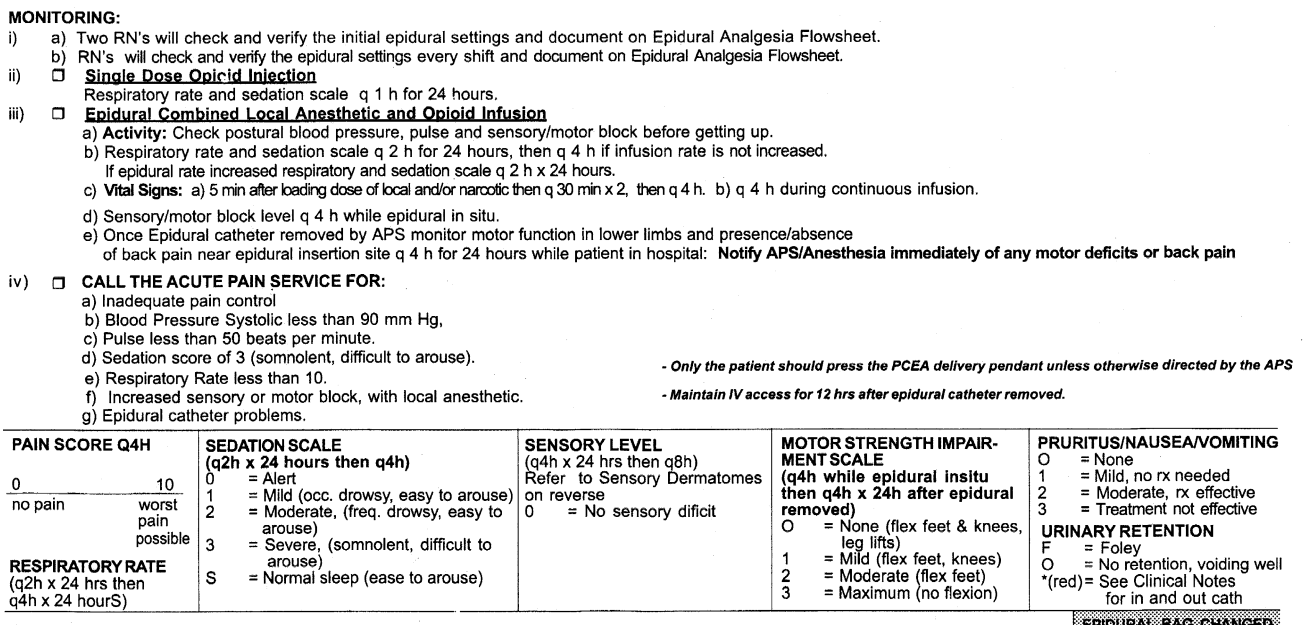
NSAID
❑ **Ketorolac 15 mg IV q 8 h x 6 doses**
❑ Ketorolac 15 mg IV q 6 h x 8 doses
❑ Celecoxib 200 mg PO tablet bid x 10 doses

Acetaminophen
D/C all other Acetaminophen orders.
Max daily doses of acetaminophen from all sources = 4 g (i.e., 12 x 325 mg, 8 x 500 mg, 6x650 mg)
❑ **Acetaminophen 1000 mg PO tablet q 6 h x 8 doses**
❑ Acetaminophen 1000 mg PO tablet q 6 h X 20 doses then q 6 h PRN
❑ Acetaminophen Suppository 1300 mg PR q 8 h X 6 doses
❑ Acetaminophen 650 mg PO tablet q 6 h X 8 doses
❑ Acetaminophen 650 mg PO tablet q 6 h X 20 doses then q 6 h PRN
❑ Acetaminophen 960 mg elixir via feeding tube q 6 h X 8 doses

(For TGH Only) When Epidural Removed by Anesthesia (APS), start oral analgesics as below:
❒ **(Percocet®) Oxycodone 5 mg w/ Acetaminophen 325 mg 1 – 2 tabs PO q 3 H PRN (max 12 tablets/24 h)**
❒ (Oxy IR®) Oxycodone Immediate Release 5 – 10 mg PO tablet q 2 h PRN
❒ (Statex®) Morphine Immediate release 10 mg PO tablet q 3 h PRN
❑ (Statex®) Morphine Immediate release 10-20 mg PO tablet / feeding tube solution q 3 h PRN
❑ Hydromorphone elixir 2-4 mg PO tablet / feeding tube solution q 3 h PRN
❒ Acetaminophen 640 mg elixir via feeding tube q 4 h PRN

When Patient tolerating fluids well, start following Bowel Medication:
❒ Docusate Sodium (Colace®) 100 mg PO/elixir via feeding tube BID
❒ Senokot® 2 tabs (8.6 mg Senna/tablet) PO q 12 h

Anesthesia (APS) will remove epidural Catheter. Maintain IV access for 12 hours after epidural catheter removal



MONITORING:

i) a) Two RN's will check and verify the initial epidural settings and document on Epidural Analgesia Flowsheet.
b) RN's will check and verify the epidural settings every shift and document on Epidural Analgesia Flowsheet.

ii) ❒ **Single Dose Opicid Injection**
Respiratory rate and sedation scale q 1 h for 24 hours.

iii) ❒ **Epidural Combined Local Anesthetic and Opioid Infusion**
a) **Activity:** Check postural blood pressure, pulse and sensory/motor block before getting up.
b) Respiratory rate and sedation scale q 2 h for 24 hours, then q 4 h if infusion rate is not increased.
If epidural rate increased respiratory and sedation scale q 2 h x 24 hours.
c) **Vital Signs:** a) 5 min after loading dose of local and/or narcotic then q 30 min x 2, then q 4 h. b) q 4 h during continuous infusion.
d) Sensory/motor block level q 4 h while epidural in situ.
e) Once Epidural catheter removed by APS monitor motor function in lower limbs and presence/absence of back pain near epidural insertion site q 4 h for 24 hours while patient in hospital: **Notify APS/Anesthesia immediately of any motor deficits or back pain**

iv) ❒ **CALL THE ACUTE PAIN SERVICE FOR:**
a) Inadequate pain control
b) Blood Pressure Systolic less than 90 mm Hg,
c) Pulse less than 50 beats per minute.
d) Sedation score of 3 (somnolent, difficult to arouse).
e) Respiratory Rate less than 10.
f) Increased sensory or motor block, with local anesthetic.
g) Epidural catheter problems.

- Only the patient should press the PCEA delivery pendant unless otherwise directed by the APS

- Maintain IV access for 12 hrs after epidural catheter removed.

PAIN SCORE Q4H	**SEDATION SCALE**	**SENSORY LEVEL**	**MOTOR STRENGTH IMPAIRMENT SCALE**	**PRURITUS/NAUSEA/VOMITING**
0 — 10 no pain — worst pain possible	**(q2h x 24 hours then q4h)** 0 = Alert 1 = Mild (occ. drowsy, easy to arouse) 2 = Moderate, (freq. drowsy, easy to arouse) 3 = Severe, (somnolent, difficult to arouse) S = Normal sleep (ease to arouse)	(q4h x 24 hrs then q8h) Refer to Sensory Dermatomes on reverse 0 = No sensory dificit	**(q4h while epidural insitu then q4h x 24h after epidural removed)** O = None (flex feet & knees, leg lifts) 1 = Mild (flex feet, knees) 2 = Moderate (flex feet) 3 = Maximum (no flexion)	O = None 1 = Mild, no rx needed 2 = Moderate, rx effective 3 = Treatment not effective **URINARY RETENTION** F = Foley O = No retention, voiding well *(red) = See Clinical Notes for in and out cath
RESPIRATORY RATE (q2h x 24 hrs then q4h x 24 hourS)				

FIG. 46.17. Nursing protocol for monitoring patients with thoracic epidural infusions in the intensive care unit or on the post-operative surgical ward (image courtesy of the Toronto General Hospital).

Clinical Case Discussion

Case

A 39-year-old man is scheduled for bronchoscopy and right lower lobectomy. He presented to his family doctor 4 months earlier with hemoptosis, diagnosis was delayed because of his frequent non-attendance. A CT-guided fine needle biopsy established the diagnosis as non-small cell carcinoma. He remains a heavy smoker of both marijuana and tobacco and has a 12-year history of heroin addiction. He is presently maintained on oral methadone but admits to occasional intravenous heroin use. Past medical history includes an exploratory right thoracotomy for a knife wound to the chest 5 years ago but no significant illnesses. He is very concerned about post-thoracotomy pain, stating that he suffered greatly after his previous thoracotomy. Clinical examination reveals a thin clubbed man who is very anxious. Pulmonary functions tests show a FEV_1 of 65% predicted and a DLCO of 68% predicted. A full blood count, renal function and clotting screen are normal.

Questions

- What additional information might be useful in planning his anaesthetic?
  - Current dose of methadone (substantiated by primary care physician or rehabilitation unit).
  - Ability to tolerate NSAIDs.
  - Intravenous drug use associated infectious diseases status (HIV, Hep C and Hep B).
- How will his long-term opioid intake affect his postoperative analgesia?
  - Tolerance to opioid analgesics impacts on the ability to treat acute pain adequately and he may experience more post-operative pain.
  - Need for maintenance dose of opioids, either orally or by infusion to avoid acute withdrawal.
- What are the post-operative analgesic options?
  - Establish the appropriate route and equivalent dose of the opioid to be administered peri-operatively. Ensure patient receives at least 50% of the equivalent dose to avoid acute withdrawal symptoms. Use a multimodal approach with a regional technique combined with regular acetaminophen and NSAIDs.
  - Choice of regional technique includes thoracic epidural or paravertebral and would be influenced by factors as given in Table 46.3 but a thoracic epidural with a lipophilic opioid offers the best analgesic option.
  - Consideration of gabapentin pre-operative as a single oral dose.
  - If a regional technique is not possible, a ketamine bolus in theatre followed by a ketamine infusion supplemented to an opioid IV-PCA system.

References

1. Griffith DPG, Diamond AW, Cameron JD. Postoperative epidural analgesia following thoracic surgery: a feasibility study. Br J Anaesth. 1975;47:48–55.

2. Shuman RL, Peters RM. Epidural anesthesia following thoracotomy in patients with chronic obstructive airway disease. J Thorac Cardiovasc Surg. 1976;71:82–8.
3. Cook TM, Riley RH. Analgesia following thorocotomy: a survey of Australian practice. Anaesth Intensive Care. 1997;25:520–4.
4. Cook TM, Counsell D, Wildsmith JA; Royal College of Anaesthetists Third National Audit Project. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. Br J Anaesth. 2009;102:179–90.
5. Counsell D. Complications after perioperative central neuraxial blocks. In: The Third National Audit Project (NAP3), editor. Major complications of central neuraxial block in the United Kingdom. London: The Royal College of Anaesthetists; 2009. p. 101–11.
6. Horlocker TT, Wedel DJ, Benzon H, et al. Regional anesthesia in the anticoagulated patient: defining the risks (The Second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). Reg Anesth Pain Med. 2003;28:172–97.
7. Howard-Alpe GM, de Bono J, Hudsmith L, et al. Coronary artery stents and non-cardiac surgery. Br J Anaesth. 2007;98:560–74.
8. Chassot PG, Delabys A, Spahn DR. Perioperative antiplatelet therapy: the case for continuing therapy in patients at risk of myocardial infarction. Br J Anaesth. 2007;99:316–28.
9. Newsome LT, Weller RS, Gerancher JC, et al. Coronary artery stents: II. Perioperative considerations and management. Anesth Analg. 2008;107:570–90.
10. Joshi GP, Bonnet F, Shah R, et al. A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. Anesth Analg. 2008;107:1026–40.
11. Davies RG, Myles PS, Graham JM. A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy – a systematic review and meta-analysis of randomized trials. Br J Anaesth. 2006;96:418–26.
12. Eghert LD, Battit GE, Welch CE, Bartlett MK. Reduction of postoperative pain by encouragement and instruction of patients. N Engl J Med. 1964;270:825–7.
13. Anonymous. The report of the Public Inquiry into children's heart surgery at the Bristol Royal Infirmary 1984–1995: learning from Bristol. London: TSO; 2001.
14. Pennefather SH, Gilby S, Danecki A, Russell GN. The changing practice of thoracic epidural analgesia in the United Kingdom: 1997-2004. Anaesthesia. 2006;61:363–9.
15. Loan WB, Morrison JD. The incidence and severity of postoperative pain. Br J Anaesth. 1967;39:695–8.
16. Macintosh RR, Mushin WW. Anaesthetics research in wartime. Medical Times. 1945;253–5.
17. Mark JBD, Brodsky JB. Ipsilateral shoulder pain following thoracic operations. Anesthesiology. 1993;79:192.
18. Burgess FW, Anderson DM, Colonna D, Sborov MJ, Cavanaugh DG. Ipsilateral shoulder pain following thoracic surgery. Anesthesiology. 1993;78:365–8.
19. Scawn ND, Pennefather SH, Soorae A, Wang JY, Russell GN. Ipsilateral shoulder pain after thoracotomy with epidural analgesia: the influence of phrenic nerve infiltration with lidocaine. Anesth Analg. 2001;93:260–4.
20. Kirchner A, Birklein F, Stefan H, Handwerker HO. Left vagus nerve stimulation suppresses experimentally induced pain. Neurology. 2000;55:1167–71.
21. Mitra S, Sinatra RS. Perioperative management of acute pain in the opioid-dependent patient. Anesthesiology. 2004;101:212–7.
22. Bohn LM, Gainetdinov RR, Lin FT, Lefkowitz RJ, Caron MG. Mu-opioid receptor desensitization by beta-arrestin-2 determines morphine tolerance but not dependence. Nature. 2000;408:720–3. vm 1997;278:58–63.
23. Nestler EJ, Aghajanian GK. Molecular and cellular basis of addiction. Science. 1997;278:58–63.
24. Nestler EJ. Molecular basis of long-term plasticity underlying addiction. Nat Rev Neurosci. 2001;2:119–28.
25. Mayer DJ, Mao J, Holt J, Price DD. Cellular mechanisms of neuropathic pain, morphine tolerance, and their interactions. Proc Natl Acad Sci USA. 1999;96:7731–6.
26. Compton P, Charuvastra VC, Kintaudi K, Ling W. Pain responses in methadone-maintained opioid abusers. J Pain Symptom Manage. 2000;20:237–45.
27. Laulin JP, Célèrier E, Larcher A, Le Moal M, Simonnet G. Opiate tolerance to daily heroin administration: an apparent phenomenon associated with enhanced pain sensitivity. Neuroscience. 1999;89:631–6.
28. Crile GW. The kinetic theory of shock and its prevention through anoci-association (shockless operation). Lancet. 1913;185:7–13.
29. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. Nature. 1983;306:686–8.
30. Kissin I. Preemptive analgesia. Anesthesiology. 2000;93:1138–43.
31. Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. Anesthesiology. 2002;96:725–41.
32. Bong CL, Samuel M, Ng JM, Ip-Yam C. Effects of preemptive epidural analgesia on post-thoracotomy pain. J Cardiothorac Vasc Anesth. 2005;19:786–93.
33. Hurley RW, Adams MC. Sex, gender, and pain: an overview of a complex field. Anesth Analg. 2008;107:309–17.
34. Riley III JL, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. Pain. 1998;74:181–7.
35. Pickering G, Jourdan D, Eschalier A, Dubray C. Impact of age, gender and cognitive functioning on pain perception. Gerontology. 2002;48:112–8.
36. Gijsbers K, Nicholson F. Experimental pain thresholds influenced by sex of experimenter. Percept Mot Skills. 2005;101: 803–7.
37. Sullivan MJ, Rodgers WM, Kirsch I. Catastrophizing, depression and expectancies for pain and emotional distress. Pain. 2001;91:147–54.
38. Keefe FJ, Lefebvre JC, Egert JR, Affleck G, Sullivan MJ, Caldwell DS. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. Pain. 2000;87:325–34.
39. Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. Anesthesiology. 2009;111:657–77.
40. Bellville JW, Forrest Jr WH, Miller E, Brown Jr BW. Influence of age on pain relief from analgesics. A study of postoperative patients. JAMA. 1971;217:1835–41.
41. Yokoyama M, Hanazaki M, Fujii H, et al. Correlation between the distribution of contrast medium and the extent of blockade during epidural anesthesia. Anesthesiology. 2004;100:1504–10.
42. Hirabayashi Y, Shimizu R. Effect of age on extradural dose requirement in thoracic extradural anaesthesia. Br J Anaesth. 1993;71:445–6.

43. Perry F, Parker RK, White PF, Clifford PA. Role of psychological factors in postoperative pain control and recovery with patient-controlled analgesia. Clin J Pain. 1994;10:57–63.
44. Rhudy JL, Meagher MW. Fear and anxiety: divergent effects on human pain thresholds. Pain. 2000;84:65–75.
45. Bachiocco V, Morselli-Labate AM, Rusticali AG, Bragaglia R, Mastrorilli M, Carli G. Intensity, latency and duration of post-thoracotomy pain: relationship to personality traits. Funct Neurol. 1990;5:321–32.
46. Caumo W, Schmidt AP, Schneider CN, et al. Preoperative predictors of moderate to intense acute postoperative pain in patients undergoing abdominal surgery. Acta Anaesthesiol Scand. 2002;46:1265–71.
47. Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Characteristics and prediction of early pain after laparoscopic cholecystectomy. Pain. 2001;90:261–9.
48. Tasmuth T, Estlanderb AM, Kalso E. Effect of present pain and mood on the memory of past postoperative pain in women treated surgically for breast cancer. Pain. 1996;68:343–7.
49. Landreneau RJ, Hazelrigg SR, Mack MJ, et al. Postoperative pain-related morbidity: video-assisted thoracic surgery versus thoracotomy. Ann Thorac Surg. 1993;56:1285–9.
50. Iwasaki A, Hamatake D, Shirakusa T. Biosorbable poly-L-lactide rib-connecting pins may reduce acute pain after thoracotomy. Thorac Cardiovasc Surg. 2004;52:49–53.
51. Bethencourt DM, Holmes EC. Muscle-sparing posterolateral thoracotomy. Ann Thorac Surg. 1988;45:337–9.
52. Ginsberg RJ. Alternative (muscle-sparing) incisions in thoracic surgery. Ann Thorac Surg. 1993;56:752–4.
53. Fry WA. Thoracic incisions. Chest Surg Clin N Am. 1995;5:177–88.
54. Khan IH, McManus KG, McCraith A, McGuigan JA. Muscle sparing thoracotomy: a biomechanical analysis confirms preservation of muscle strength but no improvement in wound discomfort. Eur J Cardiothorac Surg. 2000;18:656–61.
55. Ochroch EA, Gottschalk A, Augoustides JG, et al. Pain and physical function are similar following axillary, muscle-sparing vs posterolateral thoracotomy. Chest. 2005;128:2664–70.
56. Benedetti F, Vighetti S, Ricco C, et al. Neurophysiologic assessment of nerve impairment in posterolateral and muscle-sparing thoracotomy. J Thorac Cardiovasc Surg. 1998;115:841–7.
57. Macchiarini P, Ladurie FL, Cerrina J, et al. Clamshell or sternotomy for double lung or heart-lung transplantation? Eur J Cardiothorac Surg. 1999;15:333–9.
58. Boulanger A, Choinière M, Roy D, et al. Comparison between patient-controlled analgesia and intramuscular meperidine after thoracotomy. Can J Anaesth. 1993;40:409–15.
59. Ballantyne JC, Carr DB, Chalmers TC, et al. Postoperative patient-controlled analgesia: meta-analyses of initial randomized control trials. J Clin Anesth. 1993;5:182–93.
60. Bullingham RES. Optimum management of postoperative pain. Drugs. 1985;29:376–86.
61. Bullingham RES. Postoperative pain. Postgrad Med J. 1984;60: 847–51.
62. Ballantyne JC, Carr DB, deFerranti S, et al. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. Anesth Analg. 1998;86:598–612.
63. Guignard B, Bossard AE, Coste C, et al. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. Anesthesiology. 2000;93:409–17.
64. Rømsing J, Møiniche S, Østergaard D, Dahl JB. Local infiltration with NSAIDs for postoperative analgesia: evidence for a peripheral analgesic action. Acta Anaesthesiol Scand. 2000;44:672–83.
65. Bjørkman R, Hedner T, Hallman KM, Henning M, Hedner J. Localisation of the central antinociceptive effects of diclofenac in the rat. Brain Res. 1992;590:66–73.
66. Vanegas H, Schaible HG. Prostaglandins and cyclooxygenases [correction of cycloxygenases] in the spinal cord. Prog Neurobiol. 2001;64:327–63.
67. Hawkey CJ. Non-steroidal anti-inflammatory drugs and peptic ulcers. BMJ. 1990;300:278–84.
68. Souter AJ, Fredman B, White PF. Controversies in the perioperative use of nonsterodial antiinflammatory drugs. Anesth Analg. 1994;79:1178–90.
69. Møiniche S, Rømsing J, Dahl JB, Tramèr MR. Nonsteroidal antiinflammatory drugs and the risk of operative site bleeding after tonsillectomy: a quantitative systematic review. Anesth Analg. 2003;96:68–77.
70. Appadurai IR, Power I. NSAIDS in the postoperative period. Use with caution in elderly people. BMJ. 1993;307:257.
71. Gibson P, Weadington D, Winney RJ. NSAIDS in the postoperative period. Clinical experience confirms risk. BMJ. 1993;307:257–8.
72. Keenan DJ, Cave K, Langdon L, Lea RE. Comparative trial of rectal indomethacin and cryoanalgesia for control of early post-thoracotomy pain. BMJ. 1983;287:1335–7.
73. Pavy T, Medley C, Murphy DF. Effect of indomethacin on pain relief after thoracotomy. Br J Anaesth. 1990;65:624–7.
74. Rhodes M, Conacher I, Morritt G, Hilton C. Nonsteroidal anti-inflammatory drugs for postthoracotomy pain. A prospective controlled trial after lateral thoracotomy. J Thorac Cardiovasc Surg. 1992;103:17–20.
75. Bigler D, Moller J, Kamp-Jensen M, Berthelsen P, Hjortso NC, Kehlet H. Effect of piroxicam in addition to continuous thoracic epidural bupivacaine and morphine on postoperative pain and lung function after thoracotomy. Acta Anaesthesiol Scand. 1992;36:647–50.
76. Barak M, Ziser A, Katz Y. Thoracic epidural local anesthetics are ineffective in alleviating post-thoracotomy ipsilateral shoulder pain. J Cardiothorac Vasc Anesth. 2004;18:458–60.
77. Goppelt-Struebe M. Regulation of prostaglandin endoperoxide synthase (cyclooxygenase) isoenzyme expression. Prostaglandins Leukot Essent Fatty Acids. 1995;52:213–22.
78. Tröster A, Sittl R, Singler B, Schmelz M, Schüttler J, Koppert W. Modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by parecoxib in humans. Anesthesiology. 2006;105:1016–23.
79. Einhorn TA. Cox-2: where are we in 2003? – The role of cyclooxygenase-2 in bone repair. Arthritis Res Ther. 2003;5: 5–7.
80. Glassman SD, Rose SM, Dimar JR, Puno RM, Campbell MJ, Johnson JR. The effect of postoperative nonsteroidal anti-inflammatory drug administration on spinal fusion. Spine. 1998; 23:834–8.
81. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet. 2005;365:475–81.

82. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ. 2005;330:1366.
83. Ott E, Nussmeier NA, Duke PC, et al. Efficacy and safety of the cyclooxygenase 2 inhibitors parecoxib and valdecoxib in patients undergoing coronary artery bypass surgery. J Thorac Cardiovasc Surg. 2003;125:1481–92.
84. Nussmeier NA, Whelton AA, Brown MT, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med. 2005;352:1081–91.
85. Nussmeier NA, Whelton AA, Brown MT, et al. Safety and efficacy of the cyclooxygenase-2 inhibitors parecoxib and valdecoxib after noncardiac surgery. Anesthesiology. 2006;104:518–26.
86. Joshi GP, Gertler R, Fricker R. Cardiovascular thromboembolic adverse effects associated with cyclooxygenase-2 selective inhibitors and nonselective antiinflammatory drugs. Anesth Analg. 2007;105:1793–804.
87. Flower RJ, Vane JR. Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). Nature. 1972;240:410–1.
88. Tjølsen A, Lund A, Hole K. Antinociceptive effect of paracetamol in rats is partly dependent on spinal serotonergic systems. Eur J Pharmacol. 1991;193:193–201.
89. Honoré P, Buritova J, Besson JM. Aspirin and acetaminophen reduced both Fos expression in rat lumbar spinal cord and inflammatory signs produced by carrageenin inflammation. Pain. 1995;63:365–75.
90. Remy C, Marret E, Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. Br J Anaesth. 2005;94:505–13.
91. Montgomery JE, Sutherland CJ, Kestin IG, Sneyd JR. Morphine consumption in patients receiving rectal paracetamol and diclofenac alone and in combination. Br J Anaesth. 1996;77:445–7.
92. Seymor RA, Kelly PJ, Hawkesford JE. The efficacy of ketoprofen and paracetamol (acetaminophen) in postoperative pain after third molar surgery. Br J Clin Pharmacol. 1996;41:581–5.
93. Mac TB, Girard F, Chouinard P, et al. Acetaminophen decreases early post-thoracotomy ipsilateral shoulder pain in patients with thoracic epidural analgesia: a double-blind placebo-controlled study. J Cardiothorac Vasc Anesth. 2005;19:475–8.
94. Dahl V, Ræder JC. Non-opioid postoperative analgesia. Acta Anaesthesiol Scand. 2000;44:1191–203.
95. Hernández-Palazón J, Tortosa JA, Martínez-Lage JF, Pérez-Flores D. Intravenous administration of propacetamol reduces morphine consumption after spinal fusion surgery. Anesth Analg. 2001;92:1473–6.
96. Cattabriga I, Pacini D, Lamazza G, et al. Intravenous paracetamol as adjunctive treatment for postoperative pain after cardiac surgery: a double blind randomized controlled trial. Eur J Cardiothorac Surg. 2007;32:527–31.
97. Lahtinen P, Kokki H, Hendolin H, Hakala T, Hynynen M. Propacetamol as adjunctive treatment for postoperative pain after cardiac surgery. Anesth Analg. 2002;95:813–9.
98. Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. Pain. 1995;62:259–74.
99. Célèrier E, Rivat C, Jun Y, et al. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. Anesthesiology. 2000;92:465–72.
100. Guillou N, Tanguy M, Seguin P, Branger B, Campion JP, Mallédant Y. The effects of small-dose ketamine on morphine consumption in surgical intensive care unit patients after major abdominal surgery. Anesth Analg. 2003;97:843–7.
101. Michelet P, Guervilly C, Hélaine A, et al. Adding ketamine to morphine for patient-controlled analgesia after thoracic surgery: influence on morphine consumption, respiratory function, and nocturnal desaturation. Br J Anaesth. 2007;99:396–403.
102. Suzuki M, Haraguti S, Sugimoto K, Kikutani T, Shimada Y, Sakamoto A. Low-dose intravenous ketamine potentiates epidural analgesia after thoracotomy. Anesthesiology. 2006;105:111–9.
103. Serpell MG. Gabapentin in neuropathic pain syndromes: a randomised, double-blind, placebo-controlled trial. Pain. 2002;99:557–66.
104. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus Muller L. Gabapentin for the treatment of postherpetic neuralgia. JAMA. 1998;280:1837–42.
105. Maneuf YP, Gonzalez MI, Sutton KS, Chung FZ, Pinnock RD, Lee K. Cellular and molecular action of the putative GABA-mimetic, gabapentin. Cell Mol Life Sci. 2003;60:742–50.
106. Kong VK, Irwin MG. Gabapentin: a multimodal perioperative drug? Br J Anaesth. 2007;99:775–86.
107. Mathiesen O, Møiniche S, Dahl JB. Gabapentin and postoperative pain: a qualitative and quantitative systematic review, with focus on procedure. BMC Anesthesiol. 2007;7:6.
108. Ménigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesth Analg. 2005;100:1394–9.
109. Huot MP, Chouinard P, Girard F, Ruel M, Lafontaine ER, Ferraro P. Gabapentin does not reduce post-thoracotomy shoulder pain: a randomized, double-blind placebo-controlled study. Can J Anaesth. 2008;55:337–43.
110. Jokela RM, Ahonen JV, Tallgren MK, Marjakangas PC, Korttila KT. The effective analgesic dose of dexamethasone after laparoscopic hysterectomy. Anesth Analg. 2009;109:607–15.
111. Kardash KJ, Sarrazin F, Tessler MJ, Velly AM. Single-dose dexamethasone reduces dynamic pain after total hip arthroplasty. Anesth Analg. 2008;106:1253–7.
112. Hval K, Thagaard KS, Schlichting E, Raeder J. The prolonged postoperative analgesic effect when dexamethasone is added to a nonsteroidal antiinflammatory drug (rofecoxib) before breast surgery. Anesth Analg. 2007;105:481–6.
113. Bisgaard T, Klarskov B, Kehlet H, Rosenberg J. Preoperative dexamethasone improves surgical outcome after laparoscopic cholecystectomy: a randomized double-blind placebo-controlled trial. Ann Surg. 2003;238:651–60.
114. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150:971–9.
115. Carroll D, Tramèr M, McQuay H, Nye B, Moore A. Randomization is important in studies with pain outcomes: systematic review of transcutaneous electrical nerve stimulation in acute postoperative pain. Br J Anaesth. 1996;77:798–803.
116. Stratton SA, Smith MM. Postoperative thoracotomy. Effect of transcutaneous electrical nerve stimulation on forced vital capacity. Phys Ther. 1980;60:45–7.

117. Rooney SM, Jain S, Goldiner PL. Effect of transcutaneous nerve stimulation on postoperative pain after thoracotomy. Anesth Analg. 1983;62:1010–2.
118. Warfield CA, Stein JM, Frank HA. The effect of transcutaneous electrical nerve stimulation on pain after thoracotomy. Ann Thorac Surg. 1985;39:462–5.
119. Stubbing JF, Jellicoe JA. Transcutaneous electrical nerve stimulation after thoracotomy. Pain relief and peak expiratory flow rate – a trial of transcutaneous electrical nerve stimulation. Anaesthesia. 1988;43:296–8.
120. Benedetti F, Amanzio M, Casadio C, et al. Control of postoperative pain by transcutaneous electrical nerve stimulation after thoracic operations. Ann Thorac Surg. 1997;63:773–6.
121. Erdogan M, Erdogan A, Erbil N, Karakaya HK, Demircan A. Prospective, randomized, placebo-controlled study of the effect of TENS on postthoracotomy pain and pulmonary function. World J Surg. 2005;29:1563–70.
122. Solak O, Turna A, Pekcolaklar A, et al. Transcutaneous electric nerve stimulation for the treatment of postthoracotomy pain: a randomized prospective study. Thorac Cardiovasc Surg. 2007;55:182–5.
123. Gough JD, Williams AB, Vaughan RS, Khalil JF, Butchart EG. The control of post-thoracotomy pain. A comparative evaluation of thoracic epidural fentanyl infusions and cryo-analgesia. Anaesthesia. 1988;43:780–3.
124. Muller LC, Salzer GM, Ransmayr G, Neiss A. Intraoperative cryoanalgesia for postthoracotomy pain relief. Ann Thorac Surg. 1989;48:15–8.
125. Liu SS, Richman JM, Thirlby RC, Wu CL. Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. J Am Coll Surg. 2006;203:914–32.
126. Hahnenkamp K, Theilmeier G, Van Aken HK, Hoenemann CW. The effects of local anesthetics on perioperative coagulation, inflammation, and microcirculation. Anesth Analg. 2002;94:1441–7.
127. Hardy PA. Anatomical variation in the position of the proximal intercostal nerve. Br J Anaesth. 1988;61:338–9.
128. Dryden CM, McMenemin I, Duthie DJ. Efficacy of continuous intercostal bupivacaine for pain relief after thoracotomy. Br J Anaesth. 1993;70:508–10.
129. Chan VW, Chung F, Cheng DC, Seyone C, Chung A, Kirby TJ. Analgesic and pulmonary effects of continuous intercostal nerve block following thoracotomy. Can J Anaesth. 1991;38:733–9.
130. Bachmann-Mennenga B, Biscoping J, Kuhn DF, et al. Intercostal nerve block, interpleural analgesia, thoracic epidural block or systemic opioid application for pain relief after thoracotomy? Eur J Cardiothorac Surg. 1993;7:12–8.
131. Dravid RM, Paul RE. Interpleural block – Part 1. Anaesthesia. 2007;62:1039–49.
132. Kvalheim L, Reiestad F. Intrapleural catheter in the management of postoperative pain. Anesthesiology. 1984;61:A231.
133. Miguel R, Smith R. Intrapleural, not interpleural, analgesia. Reg Anesth. 1991;16:299.
134. Baumgarten RK. Intrapleural, interpleural, or pleural block? Simpler may be better. Reg Anesth. 1992;17:116.
135. Murphy DF. Interpleural analgesia. Br J Anaesth. 1993;71: 426–34.
136. Schneider RF, Villamena PC, Harvey J, Surick BG, Surick IW, Beattie EJ. Lack of efficacy of intrapleural bupivacaine for postoperative analgesia following thoracotomy. Chest. 1993;103:414–6.
137. Miguel R, Hubbell D. Pain management and spirometry following thoracotomy: a prospective, randomized study of four techniques. J Cardiothorac Vasc Anesth. 1993;7:529–34.
138. Raffin L, Fletcher D, Sperandio M, et al. Interpleural infusion of 2% lidocaine with 1:200,000 epinephrine for postthoracotomy analgesia. Anesth Analg. 1994;79:328–34.
139. Rosenberg PH, Scheinin BM, Lepantalo MJ, Lindfors O. Continuous intrapleural infusion of bupivacaine for analgesia after thoracotomy. Anesthesiology. 1987;67:811–3.
140. Kambam JR, Hammon J, Parris WC, Lupinetti FM. Intrapleural analgesia for post-thoracotomy pain and blood levels of bupivacaine following intrapleural injection. Can J Anaesth. 1989;36:106–9.
141. Broome IJ, Sherry KM, Reilly CS. A combined chest drain and intrapleural catheter for post-thoracotomy pain relief. Anaesthesia. 1993;48:724–6.
142. Pennefather SH, Akrofi ME, Kendall JB, Russell GN, Scawn ND. Double-blind comparison of intrapleural saline and 0.25% bupivacaine for ipsilateral shoulder pain after thoracotomy in patients receiving thoracic epidural analgesia. Br J Anaesth. 2005;94:234–8.
143. Sellheim H. Verh Dtch Ges Gynak. 1906;176.
144. Eason MJ, Wyatt R. Paravertebral thoracic block-a reappraisal. Anaesthesia. 1979;34:638–42.
145. Lönnqvist PA, Hildingsson U. The caudal boundary of the thoracic paravertebral space. A study in human cadavers. Anaesthesia. 1992;47:1051–2.
146. Karmakar MK. Thoracic paravertebral block. Anesthesiology. 2001;95:771–80.
147. Nunn JF, Slavin G. Posterior intercostal nerve block for pain relief after cholecystectomy. Anatomical basis and efficacy. Br J Anaesth. 1980;52:253–60.
148. Curley J, Castillo J, Hotz J, et al. Prolonged regional nerve blockade. Injectable biodegradable bupivacaine/polyester microspheres. Anesthesiology. 1996;84:1401–10.
149. Castillo J, Curley J, Hotz J, et al. Glucocorticoids prolong rat sciatic nerve blockade in vivo from bupivacaine microspheres. Anesthesiology. 1996;85:1157–66.
150. Drager C, Benziger D, Gao F, Berde C. Prolonged intercostal nerve blockade in sheep using controlled-release of bupivacaine and dexamethasone from polymer microspheres. Anesthesiology. 1998;89:969–79.
151. Kopacz DJ, Lacouture PG, Wu D, Nandy P, Swanton R, Landau C. The dose response and effects of dexamethasone on bupivacaine microcapsules for intercostal blockade (T9 to T11) in healthy volunteers. Anesth Analg. 2003;96:576–82.
152. Grant GJ, Vermeulen K, Langerman L, Zakowski M, Turndorf H. Prolonged analgesia with liposomal bupivacaine in a mouse model. Reg Anesth. 1994;19:264–9.
153. Grant GJ, Lax J, Susser L, Zakowski M, Weissman TE, Turndorf H. Wound infiltration with liposomal bupivacaine prolongs analgesia in rats. Acta Anaesthesiol Scand. 1997;4:204–7.
154. Boogaerts JG, Lafont ND, Declercq AG, et al. Epidural administration of liposome-associated bupivacaine for the management of postsurgical pain: a first study. J Clin Anesth. 1994;6:315–20.
155. Wang CF, Djalali AG, Gandhi A, et al. An absorbable local anesthetic matrix provides several days of functional sciatic nerve blockade. Anesth Analg. 2009;108:1027–33.

156. Burns DA, Ben-David B, Chelly JE, Greensmith JE. Intercostally placed paravertebral catheterization: an alternative approach to continuous paravertebral blockade. Anesth Analg. 2008;107:339–41.
157. Sabanathan S, Smith PJ, Pradhan GN, Hashimi H, Eng JB, Mearns AJ. Continuous intercostal nerve block for pain relief after thoracotomy. Ann Thorac Surg. 1988;46:425–6.
158. Berrisford RG, Sabanathan SS. Direct access to the paravertebral space at thoracotomy. Ann Thorac Surg. 1990;49:854.
159. Soni AK, Conacher I, Waller DA, Hilton CJ. Video-assisted thoracoscopic placement of paravertebral catheters. Br J Anaesth. 1994;72:462–4.
160. Kotzé A, Scally A, Howell S. Efficacy and safety of different techniques of paravertebral block for analgesia after thoracotomy: a systematic review and metaregression. Br J Anaesth. 2009;103:626–36.
161. Berrisford RG, Sabanathan S, Mearns AJ, Clarke BJ, Hamdi A. Plasma concentrations of bupivacaine and its enantiomers during continuous extrapleural intercostal nerve block. Br J Anaesth. 1993;70:201–4.
162. Richardson J, Sabanathan S, Jones J, Shah RD, Cheema S, Mearns AJ. A prospective, randomized comparison of preoperative and continuous balanced epidural or paravertebral bupivacaine on post-thoracotomy pain, pulmonary function and stress responses. Br J Anaesth. 1999;83:387–92.
163. Association of Anaesthetists of Great Britain and Ireland. Guidelines for the management of severe local anaesthetic toxicity. August 2009. http://www.aagbi.org/publications/guidelines/docs/latoxicity07.pdf. Accessed 20 Oct 2009.
164. Resuscitation Council (UK) website. September 2009. http://www.resus.org.uk/pages/caLocalA.html. Accessed 4 July 2009.
165. Samii K, Feret J, Harari A, Viars P. Selective spinal analgesia. Lancet. 1979;1:1142.
166. Mason N, Gondret R, Junca A, Bonnet F. Intrathecal sufentanil and morphine for post-thoracotomy pain relief. Br J Anaesth. 2001;86:236–40.
167. Liu N, Kuhlman G, Dalibon N, Moutafis M, Levron JC, Fischler M. A randomized, double-blinded comparison of intrathecal morphine, sufentanil and their combination versus IV morphine patient-controlled analgesia for postthoracotomy pain. Anesth Analg. 2001;92:31–6.
168. Neustein SM, Cohen E. Intrathecal morphine during thoracotomy, Part II: effect on postoperative meperidine requirements and pulmonary function tests. J Cardiothorac Vasc Anesth. 1993;7:157–9.
169. Liu M, Rock LM, Grass JA, et al. Double-blind randomized evaluation of intercostal nerve blocks as an adjuvant to subarachnoid administered morphine for post-thoracotomy analgesia. Reg Anesth. 1995;20:418–25.
170. Sudarshan G, Browne B, Matthews J, Conacher I. Intrathecal fentanyl for post-thoracotomy pain. Br J Anaesth. 1995;75:19–22.
171. Gray JR, Fromme GA, Nauss LA, Wang JK, Ilstup DM. Intrathecal morphine for postthoracotomy pain. Anesth Analg. 1986;65:873–6.
172. Cohen E, Neustein SM. Intrathecal morphine during thoracotomy, Part I: effect on intraoperative enflurane requirements. J Cardiothorac Vasc Anesth. 1993;7:154–6.
173. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology. 1984;61:276–310.
174. Ng A, Swanevelder J. Pain relief after thoracotomy: is epidural analgesia the optimal technique? Br J Anaesth. 2007;98:159–62.
175. Sicard A. Les injections medicamenteuses extra-durales par voie sacrococcygienne. Compt Rend Soc De Biol. 1901;53:396–8.
176. Pagés F. Anesthesia metamerica. Rev Esp Chir. 1921;3:3–30.
177. Dogliotti AM. A new method of block: segmental peridural spinal anesthesia. Am J Surg. 1933;20:107–18.
178. Logas WG, el-Baz N, el-Ganzouri A, et al. Continuous thoracic epidural analgesia for postoperative pain relief following thoracotomy: a randomized prospective study. Anesthesiology. 1987;67:787–91.
179. Muneyuki M, Shirai K, Inamoto A. Roentgenographic analysis of the positions of catheters in the epidural space. Anesthesiology. 1970;33:19–24.
180. Motamed C, Farhat F, Rémérand F, Stéphanazzi J, Laplanche A, Jayr C. An analysis of postoperative epidural analgesia failure by computed tomography epidurography. Anesth Analg. 2006;103:1026–32.
181. Königsrainer I, Bredanger S, Drewel-Frohnmeyer R, et al. Audit of motor weakness and premature catheter dislodgement after epidural analgesia in major abdominal surgery. Anaesthesia. 2009;64:27–31.
182. Conacher ID, Paes ML, Jacobson L, Phillips PD, Heaviside DW. Epidural analgesia following thoracic surgery. Anaesthesia. 1983;38:546–51.
183. Kaneko M, Saito Y, Kirihara Y, Collins JG, Kosaka Y. Synergistic antinociceptive interaction after epidural coadministration of morphine and lidocaine in rats. Anesthesiology. 1994;80:137–50.
184. Curatolo M, Schnider TW, Petersen-Felix S, et al. A direct search procedure to optimize combinations of epidural bupivacaine, fentanyl, and clonidine for postoperative analgesia. Anesthesiology. 2000;92:325–37.
185. Mahon SV, Berry PD, Jackson M, Russell GN, Pennefather SH. Thoracic epidural infusions for post-thoracotomy pain: are fentanyl-bupivacaine mixtures better than fentanyl alone? Anaesthesia. 1999;54:641–6.
186. Tan CNH, Guha A, Scawn NDA, Pennefather SH, Russell GN. Optimal concentration of epidural fentanyl in bupivacaine 0.1% after thoracotomy. Br J Anaesth. 2004;92:670–4.
187. Niemi G, Breivik H. Epinephrine markedly improves thoracic epidural analgesia produced by a small-dose infusion of ropivacaine, fentanyl, and epinephrine after major thoracic or abdominal surgery: a randomized, double-blinded crossover study with and without epinephrine. Anesth Analg. 2002;94:1598–605.
188. Eisenach JC, De Kock M, Klimscha W. alpha(2)-Adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). Anesthesiology. 1996;85:655–74.
189. Visser WA, Liem TH, van Egmond J, Gielen MJ. Extension of sensory blockade after thoracic epidural administration of a test dose of lidocaine at three different levels. Anesth Analg. 1998;86:332–5.
190. Lee CJ, Jeon Y, Lim YJ, et al. The influence of neck flexion and extension on the distribution of contrast medium in the high thoracic epidural space. Anesth Analg. 2007;104:1583–6.
191. Fratacci MD, Kimball WR, Wain JC, Kacmarek RM, Polaner DM, Zapol WM. Diaphragmatic shortening after thoracic surgery in humans. Effects of mechanical ventilation and thoracic epidural anesthesia. Anesthesiology. 1993;79:654–65.

192. Simonneau G, Vivien A, Sartene R, et al. Diaphragm dysfunction induced by upper abdominal surgery. Role of postoperative pain. Am Rev Respir Dis. 1983;128:899–903.
193. Dureuil B, Viires N, Cantineau JP, Aubier M, Desmonts JM. Diaphragmatic contractility after upper abdominal surgery. J Appl Physiol. 1986;61:1775–80.
194. Torres A, Kimball WR, Qvist J, et al. Sonomicrometric regional diaphragmatic shortening in awake sheep after thoracic surgery. J Appl Physiol. 1989;67:2357–68.
195. Polaner DM, Kimball WR, Fratacci MD, Wain JC, Zapol WM. Thoracic epidural anesthesia increases diaphragmatic shortening after thoracotomy in the awake lamb. Anesthesiology. 1993;79:808–16.
196. Manikian B, Cantineau JP, Bertrand M, Kieffer E, Sartene R, Viars P. Improvement of diaphragmatic function by a thoracic extradural block after upper abdominal surgery. Anesthesiology. 1988;68:379–86.
197. Warner DO, Warner MA, Ritman EL. Human chest wall function during epidural anesthesia. Anesthesiology. 1996;85:761–73.
198. Richter A, Cederholm I, Jonasson L, Mucchiano C, Uchto M, Janerot-Sjoberg B. Effect of thoracic epidural analgesia on refractory angina pectoris: long-term home self-treatment. J Cardiothorac Vasc Anesth. 2002;16:679–84.
199. Gramling-Babb P, Miller MJ, Reeves ST, Roy RC, Zile MR. Treatment of medically and surgically refractory angina pectoris with high thoracic epidural analgesia: initial clinical experience. Am Heart J. 1997;133:648–55.
200. Beattie WS, Badner NH, Choi P. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. Anesth Analg. 2001;93:853–8.
201. Oka T, Ozawa Y, Ohkubo Y. Thoracic epidural bupivacaine attenuates supraventricular tachyarrhythmias after pulmonary resection. Anesth Analg. 2001;93:253–9.
202. Oka T, Ozawa Y. Correlation between intraoperative hemodynamic variability and postoperative arrhythmias in patients with pulmonary surgery. Masui. 1999;48:118–23.
203. Ritchie AJ, Bowe P, Gibbons JR. Prophylactic digitalization for thoracotomy: a reassessment. Ann Thorac Surg. 1990;50:86–8.
204. Krowka MJ, Pairolero PC, Trastek VF, et al. Cardiac dysrhythmia following pneumonectomy: clinical correlates and prognostic significance. Chest. 1987;91:490–5.
205. Von Knorring J, Lepantalo M, Lindgren L, Lindfors O. Cardiac arrhythmias and myocardial ischemia after thoracotomy for lung cancer. Ann Thorac Surg. 1992;53:642–7.
206. Modig J, Borg T, Karlstrom G, Maripuu E, Sahlstedt B. Thromboembolism after total hip replacement: role of epidural and general anesthesia. Anesth Analg. 1983;62:174–80.
207. Sharrock NE, Cazan MG, Hargett MJ, Williams-Russo P, Wilson Jr PD. Changes in mortality after total hip and knee arthroplasty over a ten-year period. Anesth Analg. 1995;80:242–8.
208. Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ. 2000;321:1493–7.
209. Rigg JR, Jamrozik K, Myles PS, Silbert BS, et al. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. Lancet. 2002;59:276–82.
210. Giebler RM, Scherer RU, Peters J. Incidence of neurologic complications related to thoracic epidural catheterization. Anesthesiology. 1997;86:55–63.
211. Wheatley RG, Schug SA, Watson D. Safety and efficacy of postoperative epidural analgesia. Br J Anaesth. 2001;87:47–61.
212. Gustafsson LL, Schildt B, Jacobsen K. Adverse effects of extradural and intrathecal opiates: report of a nationwide survey in Sweden. Br J Anaesth. 1982;54:479–86.
213. Liu SS, Allen HW, Olsson GL. Patient-controlled epidural analgesia with bupivacaine and fentanyl on hospital wards: prospective experience with 1,030 surgical patients. Anesthesiology. 1998;88:688–95.
214. Shanker KB, Palkar NV, Nishkala R. Paraplegia following epidural potassium chloride. Anaesthesia. 1985;40:45–7.
215. Moen V, Dahlgren N, Irestedt L. Severe neurological complications after central neuraxial blockades in Sweden 1990-1999. Anesthesiology. 2004;101:950–9.
216. Gogarten W, Van Aken H, Riess H. German guidelines on regional anaesthesia and thromboembolism prophylaxis. Anaethesiologie und Intensivmedizin. 2007;48:124–9.
217. Horlocker TT, Wedel DJ. Neurological complications of spinal and epidural anesthesia. Reg Anesth Pain Med. 2000;25:83–98.
218. Stafford-Smith M. Impaired haemostasis and regional anaesthesia. Can J Anaesth. 1996;43:R129–35.
219. Meikle J, Bird S, Nightingale J, White N. Detection and management of epidural haematomas related to anaesthesia in the UK: a national survey of current practice. Br J Anaesth. 2008;101:400–4.
220. CLASP (Collaborative Low-Dose Aspirin Study in Pregnancy) Collaborative Group. CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. Lancet. 1994;343:619–29.
221. Horlocker TT, Bajwa ZH, Ashraft Z, et al. Risk assessment of hemorrhagic complications associated with nonsteroidal antiinflammatory medications in ambulatory pain clinic patients undergoing epidural steroid injection. Anesth Analg. 2002;95:1691–7.
222. Newsome LT, Kutcher MA, Royster RL. Coronary artery stents: Part I. Evolution of percutaneous coronary intervention. Anesth Analg. 2008;107:552–69.
223. Collins R, Scrimgeour A, Yusuf S, et al. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic and urologic surgery. N Engl J Med. 1988;318:1162–73.
224. Vandermeulen EP, Van Aken H, Vermylen J. Anticoagulants and spinal-epidural anesthesia. Anesth Analg. 1994;79:1165–77.
225. Greaves JD. Serious spinal cord injury due to haematomyelia caused by spinal anesthesia in a patient treated with low dose heparin. Anaesthesia. 1997;52:150–4.
226. Sandhu H, Morley-Forster P, Spadafora S. Epidural hematoma following epidural analgesia in a patient receiving unfractionated heparin for thromboprophylaxis. Reg Anesth Pain Med. 2000;25:72–5.
227. Liu SS, Mulroy MF. Neuraxial anesthesia and analgesia in the presence of standard heparin. Reg Anesth Pain Med. 1998;23:157–63.
228. Bergqvist D, Lindblad B, Matzsch T. Low molecular weight heparin for thromboprophylaxis and epidural/spinal anaesthesia – is there a risk? Acta Anaesthesiol Scand. 1992;36:605–9.
229. Tryba M, Wedel DJ. Central neuraxial block and low molecular weight heparin (enoxaparin): lessons learned from two different dosage regimes in two continents. Acta Anaesthesiol Scand. 1997;41:100–4.

230. Bromage PR, Camporesi EM, Durant PA, Nielsen CH. Nonrespiratory side effects of epidural morphine. Anesth Analg. 1982;61:490–5.
231. Yaksh TL. Spinal opiate analgesia: characteristics and principles of action. Pain. 1981;11:293–346.
232. Rawal N, Mollefors K, Axelsson K, Lingardh G, Widman B. An experimental study of urodynamic effects of epidural morphine and of naloxone reversal. Anesth Analg. 1983;62:641–7.
233. Husted S, Djurhuus JC, Husegaard HC, Jepsen J, Mortensen J. Effect of postoperative extradural morphine on lower urinary tract function. Acta Anaesthesiol Scand. 1985;29:183–5.
234. Wang J, Pennefather S, Russell G. Low-dose naloxone in the treatment of urinary retention during extradural fentanyl causes excessive reversal of analgesia. Br J Anaesth. 1998;80:565–6.
235. Goldhill DR, Whelpton R, Winyard JA, Wilkinson KA. Gastric emptying in patients the day after cardiac surgery. Anaesthesia. 1995;50:122–5.
236. Petring OU, Dawson PJ, Blake DW, et al. Normal postoperative gastric emptying after orthopaedic surgery with spinal anaesthesia and i.m. ketorolac as the first postoperative analgesic. Br J Anaesth. 1995;74:257–60.
237. Thorn SE, Wattwil M, Naslund I. Postoperative epidural morphine, but not epidural bupivacaine, delays gastric emptying on the first day after cholecystectomy. Reg Anesth. 1992;17:91–4.
238. Bonica JJ. Autonomic innervation of the viscera in relation to nerve block. Anesthesiology. 1968;29:793–813.
239. Guha A, Scawn NDA, Rogers SA, Pennefather SH, Russell GN. Gastric emptying in post thoracotomy patients receiving a thoracic fentanyl – bupivacaine epidural infusion. Eur J Anaesthesiol. 2002;19:652–7.
240. Lundberg JF, Martner J, Raner C. Dopamine or norepinephrine infusion during thoracic epidural anesthesia? Differences in hemodynamic effects and plasma catecholamine levels. Acta Anaesthesiol Scand. 2005;49:962–8.
241. Tan N, Agnew NM, Scawn ND, Pennefather SH, Chester M, Russell GN. Suprascapular nerve block for ipsilateral shoulder pain after thoracotomy with thoracic epidural analgesia: a double-blind comparison of 0.5% bupivacaine and 0.9% saline. Anesth Analg. 2002;94:199–202.
242. Danelli G, Berti M, Casati A, et al. Ipsilateral shoulder pain after thoracotomy surgery: a prospective, randomized, double-blind, placebo-controlled evaluation of the efficacy of infiltrating the phrenic nerve with 0.2%wt/vol ropivacaine. Eur J Anaesthesiol. 2007;24:596–601.
243. Ng KP, Chow YF. Brachial plexus block for ipsilateral shoulder pain after thoracotomy. Anaesth Intensive Care. 1997;25:74–6.
244. Barak M, Iaroshevski D, Poppa E, Ben-Nun A, Katz Y. Low-volume interscalene brachial plexus block for post-thoracotomy shoulder pain. J Cardiothorac Vasc Anesth. 2007;21:554–7.
245. Urmey WF, McDonald M. Hemidiaphragmatic paresis during interscalene brachial plexus block: effects on pulmonary function and chest wall mechanics. Anesth Analg. 1992;74:352–7.
246. Garner L, Coats RR. Ipsilateral stellate ganglion block effective for treating shoulder pain after thoracotomy. Anesth Analg. 1994;78:1195–6.
247. Kocabas S, Yedicocuklu D, Yuksel E, Uysallar E, Askar F. Infiltration of the sternotomy wound and the mediastinal tube sites with 0.25% levobupivacaine as adjunctive treatment for postoperative pain after cardiac surgery. Eur J Anaesthesiol. 2008;25:842–9.
248. Magnano D, Montalbano R, Lamarra M, et al. Ineffectiveness of local wound anesthesia to reduce postoperative pain after median sternotomy. J Card Surg. 2005;20:314–8.
249. McDonald SB, Jacobsohn E, Kopacz DJ, et al. Parasternal block and local anesthetic infiltration with levobupivacaine after cardiac surgery with desflurane: the effect on postoperative pain, pulmonary function, and tracheal extubation times. Anesth Analg. 2005;100:25–32.
250. Zingg U, McQuinn A, DiValentino D, et al. Minimally invasive versus open esophagectomy for patients with esophageal cancer. Ann Thorac Surg. 2009;87:911–9.
251. Perttunen K, Nilsson E, Heinonen J, Hirvisalo EL, Salo JA, Kalso E. Extradural, paravertebral and intercostal nerve blocks for post-thoracotomy pain. Br J Anaesth. 1995;75:541–7.
252. Matthews PJ, Govenden V. Comparison of continuous paravertebral and extradural infusions of bupivacaine for pain relief after thoracotomy. Br J Anaesth. 1989;62:204–5.
253. Coe A, Sarginson R, Smith MW, Donnelly RJ, Russell GN. Pain following thoracotomy. A randomised, double-blind comparison of lumbar versus thoracic epidural fentanyl. Anaesthesia. 1991;46:918–21.
254. Haak-van der Lely F, van Kleef JW, Burm AG, Bovill JG. An intra-operative comparison of lumbar with thoracic epidural sufentanil for thoracotomy. Anaesthesia. 1994;49:119–21.
255. Thomson CA, Becker DR, Messick Jr JM, et al. Analgesia after thoracotomy: effects of epidural fentanyl concentration/infusion rate. Anesth Analg. 1995;81:973–81.
256. Licker MJ, Widikker I, Robert J, et al. Operative mortality and respiratory complications after lung resection for cancer: impact of chronic obstructive pulmonary disease and time trends. Ann Thorac Surg. 2006;81:1830–7.
257. Powell ES, Pearce AC, Cook D, et al. UK pneumonectomy outcome study (UKPOS): a prospective observational study of pneumonectomy outcome. J Cardiothorac Surg. 2009;4:41.
258. Cense HA, Lagarde SM, de Jong K, et al. Association of no epidural analgesia with postoperative morbidity and mortality after transthoracic esophageal cancer resection. J Am Coll Surg. 2006;202:395–400.
259. Smedstad KG, Beattie WS, Blair WS, Buckley DN. Postoperative pain relief and hospital stay after total esophagectomy. Clin J Pain. 1992;8:149–53.
260. Whooley BP, Law S, Murthy SC, Alexandrou A, Wong J. Analysis of reduced death and complication rates after esophageal resection. Ann Surg. 2001;233:338–44.
261. Watson A, Allen PR. Influence of thoracic epidural analgesia on outcome after resection for esophageal cancer. Surgery. 1994;115:429–32.
262. Law S, Wong KH, Kwok KF, et al. Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. Ann Surg. 2004;240:791–800.
263. Michelet P, D'Journo XB, Roch A, et al. Perioperative risk factors for anastomotic leakage after esophagectomy: influence of thoracic epidural analgesia. Chest. 2005;128:3461–6.
264. Page RD, Shackcloth MJ, Russell GN, Pennefather SH. Surgical treatment of anastomotic leaks after oesophagectomy. Eur J Cardiothorac Surg. 2005;27:337–43.
265. Ikeda Y, Niimi M, Kan S, Shatari T, Takami H, Kodaira S. Clinical significance of tissue blood flow during esophagectomy by laser Doppler flowmetry. J Thorac Cardiovasc Surg. 2001;122:1101–6.

266. Al-Rawi OY, Pennefather SH, Page RD, Dave I, Russell GN. The effect of thoracic epidural bupivacaine and an intravenous adrenaline infusion on gastric tube blood flow during esophagectomy. Anesth Analg. 2008;106:884–7.
267. Michelet P, Roch A, D'Journo XB, et al. Effect of thoracic epidural analgesia on gastric blood flow after oesophagectomy. Acta Anaesthesiol Scand. 2007;51:587–94.
268. Kelly FE, Murdoch JA, Sanders DJ, Berrisford RG. Continuous paravertebral block for thoraco-abdominal oesophageal surgery. Anaesthesia. 2005;60:98–9.
269. de Leon-Casasola OA, Lema MJ. Epidural sufentanil for acute pain control in a patient with extreme opioid dependency. Anesthesiology. 1992;76:853–6.
270. de Leon-Casasola OA, Lema MJ. Epidural bupivacaine/sufentanil therapy for postoperative pain control in patients tolerant to opioid and unresponsive to epidural bupivacaine/morphine. Anesthesiology. 1994;80:303–9.
271. Rapp SE, Ready LB, Nessly ML. Acute pain management in patients with prior opioid consumption: a case-controlled retrospective review. Pain. 1995;61:195–201.
272. Swenson JD, Davis JJ, Johnson KB. Postoperative care of the chronic opioid-consuming patient. Anesthesiol Clin North America. 2005;23:37–48.
273. Fitzgibbon DR, Ready LB. Intravenous high-dose methadone administered by patient controlled analgesia and continuous infusion for the treatment of cancer pain refractory to high-dose morphine. Pain. 1997;73:259–61.
274. Carroll IR, Angst MS, Clark JD. Management of perioperative pain in patients chronically consuming opioids. Reg Anesth Pain Med. 2004;29:576–91.
275. Barrington MJ, Scott DA. Do we need to justify epidural analgesia beyond pain relief? Lancet. 2008;372:514–6.
276. Landreneau RJ, Mack MJ, Hazelrigg SR, et al. Prevalence of chronic pain. J Thorac Cardiovasc Surg. 1994;107:1079–85.
277. Ramamurthy S. Thoracic epidural nerve block. In: Waldman SD, Winnie AP, editors. Interventional pain management. Philadelphia: WB Saunders; 1996.
278. Gosling JA, Harris PF, Humpherson JR. Atlas of human anatomy. London: Churchill Livingstone; 1985.
279. Pennefather SH, Russell GN. Postthoracotomy analgesia. In: Slinger PD, editor. Progress in thoracic anaesthesia, A Society of Cardiovascular Anesthesiologist Monograph. Philadelphia: Lippincott Williams & Wilkins; 2004.
280. Gottschalk A, Cohen SP, Yang S, Ochroch EA. Preventing and treating pain after thoracic surgery. Anesthesiology. 2006;104:594–600.