Acute Pain Management for Patients Undergoing Thoracotomy

Roy G. Soto, MD, and Eugene S. Fu, MD

Department of Anesthesiology, University of South Florida College of Medicine, Tampa, Florida

Management of thoracotomy pain can be difficult, but the benefits of effective pain control are significant. A variety of modalities for treating postoperative pain after thoracotomy are available, including systemic opiates, regional analgesics, and new oral and parenteral agents. This work provides a review of the literature and recommendations for the clinician.

(Ann Thorac Surg 2003;75:1349–57)

The role of well-planned pain management has been crucial in decreasing morbidity after major thoracic surgery for lung resection. Pain is a key component in the alteration of lung function after thoracic surgery, highlighting the importance of providing effective postoperative analgesia to reduce pulmonary complications and attenuate the stress response. Pain from a thoracotomy incision is considered to be severe and intense as a consequence of tissue damage to the ribs, muscles, and peripheral nerves. Various analgesic techniques have been developed to treat postoperative thoracotomy pain; however, acute and chronic pain conditions associated with thoracotomy continue to present a problem to clinicians.

Methods

Literature review for this work was performed using the National Library of Medicine's PubMed search engine and the MDConsult journal search engine. Key words used for searching included thoracotomy, preemptive analgesia, VATS, video-assisted thoracic surgery, postthoracotomy pain, postoperative pain, and epidural.

Overview of Postoperative Pain Management

Almost 200,000 patients a year are diagnosed with bronchogenic carcinoma, and nearly one-quarter of these patients will undergo surgical resection [1]. In addition to loss of lung tissue and pulmonary reserve, postoperative thoracotomy patients experience painful wound incisions that alter chest wall mechanics [2]. Ineffective chest expansion may predispose to atelectasis, ventilation/perfusion mismatching, hypoxemia, and infection [3, 4]. Thus, the goal of the clinician is to develop an analgesic regimen that provides effective pain relief to allow postoperative thoracotomy patients the ability to maintain their functional residual capacity by deep breathing [5]. Effective clearing of secretions with cough and early mobilization can lead to quicker recovery and shorter length of hospital stay [2, 6]. Furthermore, inadequate acute postoperative pain management may contribute to the development of a chronic postthoracotomy pain syndrome [7, 8].

The pain associated with thoracotomy incisions can be difficult to target and quantify, and prior studies have evaluated chest tube pain, incisional pain, visceral pain, and pain at rest or associated with coughing or movement. In addition, pain itself is a complex phenomenon, involving multiple neurotransmitters and excitatory and inhibitory pathways.

Various pain management techniques to treat postoperative pain after thoracic surgery have been described. Controversy exists, however, on what to give, when to give it, and where to administer it. Systemic administration of opioids is the simplest and most common method to provide analgesia for postoperative pain; unfortunately, systemic opioid administration may not be adequate for treating the intense postoperative pain associated with thoracotomy. Consequently, other analgesic techniques are often implemented, including central administration of drugs to sites of action in the spinal cord through epidural or subarachnoid routes, and attempts at deposition of drugs near peripheral nerves that innervate the rib cage.

Opioids and local anesthetic agents are the pharmacologic agents most commonly used for postoperative pain management, alone or in combination, and either sytemically, regionally, or locally. Ketorolac, tramadol, COX-2 inhibitors, and ketamine are other potentially useful analgesic agents as alternatives or adjuncts to opioids. To improve the quality of analgesia, two classes of drugs can be administered concurrently to obtain a synergistic analgesic effect while minimizing the side effects of each drug (listed in Table 1) [9]. Finally, the surgical technique itself can be modified in an attempt to reduce the impact of postoperative pain.

The following discussion will briefly review the anatomy and physiology of the pain response, describe the concepts of preemptive analgesia and wind-up, and provide a review of the literature concerning the currently available pain treatment modalities and future directions in pain management.

Address reprint requests to Dr Soto, Bruce B. Downs Blvd, MDC Department of Anesthesiology, University of South Florida College of Medicine, Tampa, FL 33612; e-mail: rsoto@hsc.usf.edu.

Published by Elsevier Science Inc

0003-4975/03/$30.00
PII S0003-4975(02)04647-7

Ann Thorac Surg
2003;75:1349–57

Table 1. Adverse Effects of Analgesic Drugs

Drugs	Adverse Events
Opioids	Respiratory depression
	Nausea and vomiting
	Urinary retention
	Pruritus
Local anesthetics	Seizures
	Hypotension
	Cardiac dysrhythmias
Ketorolac	Renal impairment
	Platelet dysfunction
	Gastrointestinal bleeding
COX-2 inhibitors	Side effects minimal
Ketamine	Hallucinations
	Emergence delirium
	Catecholamine release with resulting hypertension and tachycardia
	Increased intracranial pressure
	Increased secretions

Concepts in Postoperative Pain

Pain can be defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, as described in terms of such damage. Local tissue damage results in inflammation and propagation of stimuli to the central nervous system. These stimuli are modulated by excitatory (N-methyl-D-aspartate [NMDA]) and inhibitory (opiate) pathways. Clinical and laboratory observations suggest that pain can result in hyperexcitability in the spinal cord, resulting in increasing levels of perceived pain. This process, also known as central sensitization or "wind-up," involves conduction of impulses along afferent C-fibers, and release of excitatory neurotransmitters such as glutamate and aspartate through the NMDA receptor [10–14].

Electrophysiologic animal data [15] have shown that administration of low doses of systemic morphine before noxious stimulation suppresses spinal cord hyperexcitability, whereas administration of doses after noxious stimulation does not completely blunt it. Because the NMDA receptor has been implicated in the generation and maintenance of spinal cord "wind-up," NMDA antagonists (eg, ketamine and dextromethorphan) are logical candidates for preemptive analgesia [16]. Animal experiments have shown promise, with animals treated preemptively with opiates, local anesthetic agents, or NMDA receptor antagonists showing a significant decrease in poststimulus pain [17–19].

Human studies, unfortunately, have not been uniformly promising, and indeed, the utility of preemptive analgesia in clinical medicine has been called into question. A recent qualitative and quantitative review of the literature evaluated 93 randomized clinical trials of preincisional versus postincisional pain control. Among the trials were studies of epidural, caudal, and intrathecal analgesia, as well as studies using ketamine and various other systemic medications used to evaluate the effects of preemptive analgesia. Findings of the review were that there is little, if any, experimental support for a preemptive analgesic effect in the clinical setting [20].

Chronic Postthoracotomy Pain

Up to 50% of patients undergoing thoracotomy will develop chronic pain related to the surgical site. Chronic postthoracotomy pain has been defined as a continuous dysesthetic burning and aching in the general area of the incision that persists at least 2 months after thoracotomy [21]. Although no one surgical technique has been proven to decrease the incidence of chronic pain, intercostal nerve damage due to rib retraction seems to be involved in the development of the neuralgia [22]. A recent study by Senturk and associates [23] evaluated the effect of preemptive epidural analgesia on long-term pain, and found that initiation of epidural bupivacaine/morphine before surgical incision reduced the incidence of long-term pain. Acute postoperative pain was also reduced, which, although at odds with the review of preemptive analgesia efficacy, seems to compliment the finding of Katz and associates [7] that patients with increased postoperative pain had an increased incidence of chronic postoperative pain.

Epidural Analgesia as the Mainstay of Postoperative Pain Management

Epidural analgesia has emerged as the analgesic technique of choice for postoperative thoracotomy pain management. Not only does the technique provide excellent pain control, but it also avoids much of the sedation associated with systemic opiates. Furthermore, the epidural catheter allows for continued dosing postoperatively, and avoids much of the motor blockade associated with intrathecal drug administration.

Compared with systemic administration, much lower doses of drug administered in the epidural space are needed to provide effective pain relief. Postoperative patients, for instance, can consume on the order of 50 to 100 mg of intravenous morphine during the first 24 hours postoperatively when administered by a PCA device [24]. In comparison, epidural doses of 5 mg of morphine can provide postoperative analgesia for 12 to 24 hours [25].

Commonly used opioid–local anesthetic mixtures reported in the literature include fentanyl-bupivacaine, morphine-bupivacaine, and fentanyl-ropivacaine [26–28]. Levo-bupivacaine, an isomer of bupivacaine with decreased cardiotoxicity, has also recently been used alone and in conjunction with opiates [29]. Ropivacaine has a similar onset and duration of action to bupivacaine, but it has an enhanced safety profile due to decreased cardiotoxicity and a less profound motor blockade than either bupivacaine or levo-bupivacaine.

In many clinical settings, epidural analgesia is used as often as possible, whereas systemic analgesia is reserved for situations in which epidural analgesia is unsuccessful or contraindicated (eg, coagulopathy, infection, neuro-

logic disease) [3, 5]. The belief that epidural analgesia should be routinely used for all thoracotomy patients, however, continues to be a topic of debate, as does the location of catheter insertion [30, 31].

Whereas there is evidence that suggests that epidural analgesia offers superior pain relief, not all studies have shown that epidural analgesia improves pulmonary function and reduces pulmonary complications [32–35]. Shulman and associates [32] found that when compared with systemic morphine, lumbar epidural morphine was efficacious in alleviating pain and improving respiratory function in patients who underwent lung resection. Salomaki and associates [33] compared patients receiving intravenous versus thoracic epidural fentanyl; patients in the epidural group had less fentanyl consumption and better preservation of respiratory function. In contrast, Benzon and associates [34] found that patients receiving epidural fentanyl infusion had better postoperative pain relief compared with patients receiving intravenous morphine PCA, but no beneficial effect on pulmonary function was noted. Grant and associates [36] found that both systemic and lumbar epidural fentanyl offered satisfactory analgesia with no differences in pulmonary function; the only difference was that the quantity of fentanyl consumed in the epidural group was less than the systemic group. Finally, in a meta-analysis review of 65 studies, Ballantyne and associates [37] concluded that postoperative epidural pain control may significantly decrease pulmonary morbidity.

Thoracic Versus Lumbar Catheters

Both lumbar and thoracic epidural catheters can be used for postoperative thoracotomy pain management. Despite the theoretical advantage of delivering smaller amounts of drug to provide analgesia along thoracic dermatomes only, the superiority of thoracic epidural analgesia over lumbar epidural analgesia has been called into question. In their meta-analysis of eight studies comparing thoracic versus lumbar epidural opioid administration in thoracotomy patients, Ballantyne and associates [37] found few positive findings. Guinard and associates [38] found that thoracic epidural analgesia improved pulmonary function and shortened hospital stay without differences in the quality of analgesia. In other studies, no significant differences in analgesia and pulmonary function were seen; however, less opioid was required in patients receiving thoracic epidural analgesia [39, 36]. Grant and associates [36] found that patients receiving thoracic epidural morphine required less morphine than patients receiving lumbar epidural morphine to attain similar degrees of analgesia without any intergroup differences in postoperative pulmonary function. Hurford and associates [39] found no differences in pain scores or the incidence of side effects when administering fentanyl through thoracic or lumbar epidural catheters, but patients in the lumbar epidural group required a higher infusion rate. In another study, thoracic epidural analgesia was associated with an increased incidence of ventilatory depression [40]. As a result of limited evidence confirming the benefits of thoracic versus lumbar epidural analgesia, some authors have expressed caution in using thoracic epidural analgesia on a routine basis [31, 40, 41].

It should be noted that most anesthesiologists are more comfortable placing lumbar epidural catheters because these catheters are placed below the conus medullaris [39], and experience placing obstetric labor epidurals is a commonplace procedure in all anesthesia training programs, whereas thoracic epidural experience varies between programs. With thoracic epidural placement, the risk of injuring spinal cord tissue if the dura is inadvertently punctured is theoretically greater, and placement of a thoracic epidural catheter can be technically more difficult due to the greater caudad angulation of the spinous processes.

Patient-Controlled Epidural Anesthesia

One alternative to continuous postoperative infusion of epidural opiates or local anesthetic agents has been the use of patient-controlled epidural anesthesia (PCEA). Although studies in patients undergoing orthopedic surgery suggest a decrease in total drug use [42], postthoracotomy studies comparing PCEA to continuous infusions have not yet been done. The quality of postoperative pain control has not been shown to be improved in PCEA-treated patients in orthopedics or obstetrics [43], nor has there been any benefit in overall morbidity or recovery. Considering the small doses of medications used in continuous epidural infusions and the lack of beneficial effects of PCEA, the advantage of this technique is unclear.

Epidurals and Dysrrhythmias

A recently suggested benefit to epidural placement is the potential for decreasing dysrrhythmias. Oka and associates [44] found that patients who received epidural bupivacaine had a reduced incidence of supraventricular tachyarrhythmias when compared with patients who only received epidural opiates. This reduction was thought to be due to the reduced sympathetic tone that resulted from the sympathectomy of the local anesthetic. This reduction, if borne out in future studies, could have a significant impact on the postoperative cardiac morbidity of thoracotomy patients.

Peripheral Neural Blockade

Peripheral nerve block techniques to anesthetize the chest wall have been utilized as alternatives to epidural analgesia. Many patients are not candidates for epidural analgesia because of anatomic consideration or patient refusal [46]. Adverse effects seen with systemic and epidural opioids can also be avoided by employing peripheral nerve block techniques in which only local anesthetic agents are administered. Even though nerve blocks may avoid the problems associated with opioids, complications associated with infiltration of large quantities of local anesthetic agents still exist. Specifically, because of the rich blood supply that surrounds the intercostal nerve, this type of block is associated with

Ann Thorac Surg
2003;75:1349–57

Table 2. Toxic Doses of Local Anesthetics

Anesthetic	Toxic Dose (mg/kg)
Lidocaine	5 if plain
	7 if with epinephrine
Bupivacaine	2.5
Ropivacaine	2
Levo-bupivacaine	2.5

high plasma concentrations of local anesthetic after injection. Consequently, the clinician needs to be meticulous in calculating the maximum dose of local anesthetic to administer. Toxic doses of commonly used local anesthetic agents are listed in Table 2. Manifestations of local anesthetic overdose include seizures, precipitous hypotension, and ventricular arrythmias.

Intercostal Nerve Block

Blockade of intercostal nerves interrupts C-fiber afferent transmission of impulses to the spinal cord. A single intercostal injection of a long-acting local anesthetic can provide pain relief and improve pulmonary function for up to 6 hours [46–48]. To achieve longer durations of analgesia, a continuous extrapleural intercostal nerve block technique by Sabanathan and associates [49] has been developed in which a catheter is placed percutaneously into an extrapleural pocket by the thoracic surgeon. A continuous intercostal catheter allows frequent dosing or infusions of local anesthetic agents and avoids multiple needle injections. Various studies have confirmed the analgesic efficacy of this technique [50–52]. Interestingly, Watson and associates [50] showed that a shorter-acting local anesthetic, lidocaine, was just as effective as the longer-acting agent bupivacaine. The potential advantage of using lidocaine instead of bupivacaine is that the cardiotoxicity of bupivacaine is far more dangerous than with lidocaine, especially in light of the fact that systemic absorption is great with an intercostal block. However, the advent of newer long-acting local anesthetic agents, including ropivacaine and levo-bupivacaine, has introduced new possibilities for prolonged analgesia with minimal cardiotoxicity.

Several investigators have compared extrapleural intercostal analgesia with epidural analgesia for postoperative thoracotomy pain relief in a randomized fashion [45, 53, 54]. Dauphin and associates [53] compared patients receiving either continuous lumbar epidural analgesia or continuous intercostal analgesia; they found similar pain scores in both groups, whereas patients in the intercostal group required more supplemental morphine analgesia for breakthrough pain. Richardson and associates [54] showed that there was similar analgesia in both patient groups, with vomiting, pruritus, and urinary retention occurring only in the epidural group, suggesting that intercostal analgesia may be more favorable than epidural analgesia. Kaiser and associates [45] noted that both thoracic epidural analgesia and extrapleural intercostal analgesia were safe and effective, and concluded that intercostal analgesia should be instituted in patients who do not qualify for thoracic epidural analgesia.

Intrapleural Analgesia

Local anesthetic agents can also be administered through a catheter positioned inside the pleural cavity as another modality to anesthetize intercostal nerves. The mechanism of action appears to be diffusion across the parietal pleura [55]. Interpleural analgesia is the more correct terminology to describe this anesthetic technique because the catheter lies between the parietal and visceral pleura [4]; however, the term "intrapleural analgesia" has been used synonymously. Several studies have shown limited or no improvement in analgesia with interpleural analgesia [4, 56–58]. Scheinin and associates [56], compared patients receiving interpleural analgesia plus oxycodone supplementation with a control group of patients who received systemic oxycodone alone; a decrease in opiate consumption was seen in the interpleural group during the first postoperative day, but not over a 48-hour period. Kambam and associates [57] found that interpleural analgesia improved pain control in patients receiving posterior and lateral thoracotomy incisions but not anterior thoracotomy incisions. In a placebo-controlled trial, Schneider and associates [58] found no subjective or objective clinical benefit with interpleural analgesia. Silimon and associates [4] did not demonstrate analgesic efficacy in patients undergoing anterolateral and posterolateral thoracotomies when comparing patients receiving either interpleural bupivacaine or saline. Explanations for the limited analgesic efficacy of interpleural analgesia include: (1) loss of local anesthetic through the chest tube; (2) dilution of local anesthetic with blood and exudative fluid present in the pleural cavity; (3) binding of local anesthetic with proteins; and (4) altered diffusion across the parietal pleural following surgical manipulation and inflammation [4, 59].

Systemic Treatment Options

As discussed previously, opioids have been the mainstay of postoperative pain management for decades. Unfortunately, systemic opioids can be associated with significant side effects, which has prompted the search for alternative systemic medications.

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are useful in pain states, and work by inhibiting the cyclooxygenase (COX) enzyme responsible for the release of mediators of inflammation. Ketorolac is an NSAID available in a parenteral form, and it has been shown to be an effective adjunct agent to improve the quality of intercostal and epidural analgesia [60, 61]. Nonsteroidal anti-inflammatory drugs, however, have been associated with inhibition of platelet aggregation, gastrointestinal bleeding, and renal toxicity, limiting their usefulness in clinical practice. Many of these side effects are associated with the COX-1 enzyme, and a newer class of selective

NSAIDs, the COX-2 inhibitors, has recently been introduced.

COX-2 Inhibitors

Oral COX-2 inhibitors and clinical trials with parenteral formulations have shown promise in reducing postoperative pain and in decreasing opiate requirements [62, 63]. As mentioned above, blocking COX-1 activity alters platelet function and promotes gastrointestinal bleeding, whereas blocking COX-2 inhibits production of prostaglandins that mediate inflammation and pain-signaling transmission [64]. Consequently, selective COX-2 inhibitors such as the oral celecoxib (Celebrex) and rofecoxib (Vioxx), and the parenteral parecoxib and nimesulide (both investigational, with the latter not available in the US [65]), have been developed to relieve pain and lessen the risk of gastrointestinal bleeding [66, 67]. A recent phase III trial showed that rofecoxib was well tolerated and provided analgesic efficacy comparable with other traditional nonsteroidal antiinflammatory agents for knee and hip osteoarthritis pain [68]. Experimental findings from an animal model of postoperative pain have been promising; in a rat model of incisional pain, Yamamoto and associates [69] showed the COX-2 inhibitors decreased the level of allodynia (pain perception in response to minimal stimulation).

It should be noted that case reports and early studies suggest that even COX-2 inhibitors can be associated with gastrointestinal bleeding and renal toxicity [70–73]. The incidence is rare, however, and the greatest risk seems to be in patients with preexisting peptic ulcer disease and renal impairment. Careful patient selection, therefore, would seem to be the prudent course of action when choosing these agents perioperatively.

Tramadol

Tramadol is a unique, nonopiate drug with an unclear mechanism of action. It binds to opiate receptors and inhibits epinephrine and serotonin reuptake, but lacks many of the side effects associated with other drugs with similar sites of action. A recent study in patients undergoing thoracotomy examined the effect of intraoperative tramadol infusion on postoperative pain [74]. Patients were randomized to receive either epidural morphine, systemic opiates, or tramadol bolus and infusion. Pain scores, morphine consumption, and respiratory levels were similar in the epidural morphine and tramadol groups, and superior to those in the systemic morphine group. Although not studied against a group receiving epidural local anesthetic agents, either alone or in conjunction with opiates, the findings do provide an alternative to opiates given either systemically or epidurally.

Ketamine

Ketamine confers analgesia by blocking the NMDA receptor. As discussed previously, the NMDA receptor is involved in central sensitization, making ketamine a logical choice in preemptive pain management. Clinical studies have shown that ketamine, administered by the systemic or epidural route, improves postoperative analgesia for abdominal surgery [24, 75, 76], although it is not entirely clear whether these effects reflect a preemptive action of the drug, or a direct analgesic effect. Significant side effects, however, including catecholamine release and significant cognitive impairment, limit the utility of this agent. A newly available version of ketamine, the S(+) isomer, seems to be associated with a significant decrease in side effects [77], and may prove to be more useful. To date, the role of ketamine in treating postoperative thoracotomy pain has not been investigated in a randomized fashion, but several authors suggest that ketamine may be a useful adjunct [3, 5, 78, 79].

Trends in Thoracic Pain Management Research

Paravertebral Nerve Block

Recent interest has reemerged in the management of thoracotomy pain by paravertebral nerve blockade. Blockade is achieved with a catheter placed surgically into a localized extrapleural paravertebral pocket. Several recent studies have suggested that paravertebral analgesia can be an effective alternative to epidural analgesia in thoracotomy patients [80]. Richardson and associates [81] found that when compared with patients receiving analgesia through a thoracic epidural catheter, patients in the thoracic paravertebral group had lower pain scores, less postoperative morphine consumption, and better preservation of pulmonary function. In addition, side effects such as nausea, vomiting, and hypotension were more problematic in the epidural group. Bimston and associates [82] randomized 50 patients to receive either paravertebral or epidural analgesia. Both methods of analgesia provided adequate postoperative pain, whereas urinary retention was more frequent in patients receiving epidural analgesia.

Video-Assisted Thoracic Surgery

Video-assisted thoracic surgery (VATS) has emerged as a new and exciting technique for lung biopsy and resection of peripheral lung cancer. Although there has been concern that VATS provides inadequate resection of pulmonary tumors [83], multiple studies have shown that survival of patients is the same or improved after VATS [84, 85]. Other studied benefits of the technique when compared with thoracotomy in lung cancer patients include improvement in postoperative pulmonary function, more rapid return to activity, shorter postoperative stay, shorter intraoperative time, and improved patient satisfaction [86].

Regarding perioperative pain control, Petrakis and associates [87] evaluated 95 patients who underwent video-assisted thoracoscopy and found that all patients had low pain scores. When compared with standard thoracotomy incisions, patients undergoing VATS had less postoperative pain and narcotic consumption in multiple studies [88, 86, 89]. However, a randomized trial comparing VATS with limited thoracotomy (10- to 14-cm anterolateral incisions without rib resection) for biopsy in patients with interstitial lung disease showed no differ-

ence in postoperative pain, narcotic requirements, spirometry, or operative time [90]. A more recent study [89] found a decrease in serum cytokine levels and postoperative pain in patients undergoing VATS versus those undergoing thoracotomy with a 20-cm incision and rib resection. The implications seem to be that VATS is associated with less postoperative pain and postoperative morbidity when compared with operations with a significantly greater level of surgical stimulation and tissue damage than in those with limited dissection.

Phrenic Nerve Infiltration

Patients undergoing thoracic surgery frequently complain of ipsilateral shoulder pain due to diaphragmatic irritation. This pain is often not covered with the band of analgesia achieved with epidural pain management. A recent study [91] evaluated the effect of infiltration of 10 mL of 1% lidocaine into the periphrenic fat pad at conclusion of surgery at the level of the diaphragm in patients undergoing thoracotomy. Patients receiving lidocaine had a significantly decreased incidence of ipsilateral shoulder pain and an overall reduction in pain score when compared with placebo infiltration. This may be a simple and effective technique for optimizing postoperative pain control when used in conjunction with epidural analgesia.

Cryoablation

Much of the pain associated with thoracotomy is mediated through the intercostal nerves. Bucerius and associates showed that patients undergoing minithoracotomy for minimally invasive cardiac surgery benefited from cryoablation of the intercostal nerve at the completion of surgery [92]. When compared with patients receiving perineural injections of lidocaine, the cryoablation patients had lower pain scores. Long-term numbness at the incision site was not a complaint in any of the study patients. Cryoablation seems to be a simple and effective option for patients undergoing thoracotomy, assuming that the equipment is available.

N-Type Calcium-Channel Blockers

Pain events are signaled through voltage-sensitive, calcium-channel conduction [93]. Various subtypes of calcium-channel blockers have been identified in the central nervous system, including types L and N. Traditional calcium-channel blockers, used for treating cardiac patients, interact with the L-type channel, without producing analgesia [94]. Ziconotide, a neuronal N-type channel blocker derived from the venom of the fish-hunting marine snail (*Conus magnus*), exerts its analgesic effect by hindering the influx of calcium needed to induce neurotransmitter release in the signaling of pain [93]. Currently, ziconotide is being recommended for Food and Drug Administration (FDA) approval for malignant and nonmalignant pain syndromes [95]. Both animal and clinical data suggest that ziconotide may be promising in treating acute postoperative pain [96–98]. Using a rat incisional model of postoperative pain, Wang and associates [96] found that subarachnoid ziconotide is more potent and longer acting than subarachnoid morphine. Although, the majority of the clinical data on ziconotide pertain to the treatment of chronic pain, Atanassoff and associates [98] recently published findings from a phase II trial that was the first investigation to use ziconotide for acute postoperative pain. They showed that subarachnoid ziconotide was efficacious in decreasing postoperative morphine consumption and decreasing pain scores in patients undergoing abdominal, prostate, and hip surgery, although they suggested that this was at the cost of an increase in unfavorable side effects from the ziconitide (dizziness, blurred vision, sedation), especially at higher doses. In the future, ziconotide may become a useful and widely used analgesic agent that can be administered in the epidural or subarachnoid space, in combination with local anesthetic agents or opiates.

Conclusions and Recommendations

Pain control is a significant concern in hospitalized patients, with many clinicians now considering pain to be the fifth vital sign [99]. Although a myriad of pain treatment options is available, it can be difficult to formulate a rational treatment plan based on the frequently conflicting literature. Based on the literature reviewed above, we make the following conclusions and recommendations.

Preemptive analgesia, although an attractive concept, has not been proven to provide the same benefit in patients as it has in animal experiments; therefore, a recommendation cannot be made to institute pain management before surgical stimulation. Adequate pain control in the immediate postoperative period, however, does seem to prevent the development of chronic thoracotomy pain; therefore, an effective pain plan must be developed and implemented, with the goal of having a pain-free patient at the conclusion of surgery.

Based on a review of the literature, we recommend VATS if appropriate for the patient's disease, and if the surgery avoids a large incision and dissection. When compared with mini-thoracotomies, however, the benefit of VATS on minimizing pain is not evident. Epidural analgesia is a highly effective technique, especially when combining local anesthetic agents and opiates. Although thoracic epidurals are preferred, epidural catheters placed in the lumbar region can provide excellent analgesia if the expertise required to safely place a thoracic catheter is not available. Intercostal blocks are useful for patients in whom an epidural is refused or contraindicated, although an increased risk for local anesthetic toxicity is present. COX-2 inhibitors are viable adjuncts for patients undergoing thoracic surgery, with the caveat that the patient have no history of peptic ulcer disease or renal impairment.

Treatment with tramadol and S(+) ketamine, as well as the use of paravertebral nerve blockade, intraoperative phrenic nerve infiltration, and intercostal nerve cryoablation, hold promise, but more research needs to be performed to fully explore the benefits of these modalities.

Currently, the literature does not support the use of intrapleural analgesia or patient-controlled epidural analgesia. It is too early to recommend N-type calcium-channel blockers for perioperative pain control in thoracic patients because the majority of studies involving these drugs have involved intrathecal administration with a significant incidence of side effects.

In conclusion, proper patient preparation and a comprehensive team approach to pain management, involving the surgeon and anesthesiologist, are vital for minimizing postoperative pain and morbidity and improving patient satisfaction.

References

1. Brewer RJ, Walsh GL. Anesthesia for thoracic surgery in the oncology patient. Anesthesiol Clin North Am 1998;16:605–28.
2. Richardson J, Sabanathan S, Shah R. Post-thoracotomy spirometric lung function: the effect of analgesia. J Cardiovasc Surg 1999;40:445–56.
3. Kruger M, McRae K. Pain management in cardiothoracic practice. Surg Clin North Am 1999;79:387–400.
4. Silimon M, Claus T, Huwer H, et al. Interpleural analgesia does not influence postthoracotomy pain. Anesth Analg 2000;91:44–50.
5. Peeters-Asdourian C, Gupta S. Choices in pain management following thoracotomy. Chest 1999;115(Suppl):122–4S.
6. Reilly JJ Jr. Preoperative and postoperative care of standard and high-risk surgical patients. Hematol Oncol Clin North Am 1997;11:449–59.
7. Katz J, Jackson M, Kavanagh BP, et al. Acute pain after thoracic surgery predicts long-term post-thoracotomy pain. Clin J Pain 1996;12:50–5.
8. d'Amours RH, Riegler FX, Little AG. Pathogenesis and management of persistent postthoracotomy pain. Chest Surg Clin N Am 1998;8:703–22.
9. Liu S, Angel JM, Owens BD, et al. Effects of epidural bupivacaine after thoracotomy. Reg Anesth 1995;20:303–10.
10. Wall PD. The prevention of postoperative pain. Pain 1988; 33:289–90.
11. McQuay HJ. Pre-emptive Analgesia. Br J Anaesth 1992;69: 1–3.
12. Wall PD, Woolf CJ. Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. J Physiol 1984;356:443–58.
13. Wall PD, Woolf CJ. The brief and the prolonged facilitatory effects of unmyelinated afferent input on the rat spinal cord are independently influenced by peripheral nerve section. Neuroscience 1986;17:1199–205.
14. McQuay HJ, Dickenson AH. Implications of nervous system plasticity for pain management. Anaesthesia 1990;45:101–2.
15. Woolf CJ, Wall PD. Morphine-sensitive and morphine-insensitive actions of C-fibre input on the rat spinal cord. Neurosci Lett 1986;64:221–5.
16. Dickenson AH. NMDA receptor antagonists: interactions with opioids. Acta Anaesthesiol Scand 1997;41:112–5.
17. Woolf CJ, Chong MS. Preemptive analgesia: treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993;77:362–79.
18. Woolf CJ. Evidence for a central component of post-injury hypersensitivity. Nature 1983;306:686–8.
19. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation: implications for the treatment of post-injury hypersensitivity states. Pain 1991;44: 293–9.
20. Moiniche 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.
21. Rogers ML, Duffy JP. Surgical aspects of chronic post-thoracotomy pain. Eur J Cardiothorac Surg 2000;18:711–6.
22. Rogers ML, et al. Preliminary findings in the neurophysicological assessment of intercostal nerve injury during thoracotomy. Eur J Cardiothorac Surg 2002;21:298–301.
23. Senturk M, et al. The effects of three different analgesia techniques on long-term postthoracotomy pain. Anesth Analg 2002;94:11–5.
24. Fu ES, Miguel R, Scharf JE. Preemptive ketamine decreases postoperative narcotic requirements in patients undergoing abdominal surgery. Anesth Analg 1997;84:1086–90.
25. Ferrante FM. Acute postoperative pain management. In: Longnecker DE, Tinker JH, Morgan GE Jr, eds. Principles and practice of anesthesiology, 2nd ed. St. Louis, MO: Mosby, 1998:2331–51.
26. Mahon SV, Berry PD, Jackson M, et al. Thoracic epidural infusions for post-thoracotomy pain: a comparison of fentanyl-bupivacaine mixtures vs. fentanyl alone. Anaesthesia 1999;54:641–6.
27. Fischer RL, Lubenow TR, Liceaga A, et al. Comparison of continuous epidural infusion of fentanyl-bupivacaine and morphine-bupivacaine in management of postoperative pain. Anesth Analg 1988;67:559–63.
28. Azad S, Groh J, Beyer A, et al. Continuous peridural analgesia vs patient controlled intravenous analgesia for pain therapy after thoracotomy. Anaesthetist 2000;49:9–17.
29. Foster RH, Markham A. Levobupivacaine: a review of its pharmacology and use as a local anaesthetic. Drugs 2000;59: 551–79.
30. Slinger PD. Pro. Every postthoracotomy patient deserves thoracic epidural analgesia. J Cardiothorac Vasc Anesth 1999;13:350–4.
31. Grant RP. Con. Every postthoracotomy patient does not deserve thoracic epidural analgesia. J Cardiothorac Vasc Anesth 1999;13:355–7.
32. Shulman M, Sandler AN, Bradley JW, et al. Postthoracotomy pain and pulmonary function following epidural and systemic morphine. Anesthesiology 1984;61:569–75.
33. Salomaki TE, Laitinen JO, Nuutinen LS. A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after thoracotomy. Anesthesiology 1991;75:790–5.
34. Benzon HT, Wong HY, Belavic AM, et al. A randomized double-blind comparison of epidural fentanyl infusion versus patient-controlled analgesia with morphine for postthoracotomy pain. Anesth Analg 1993;76:316–22.
35. Grant RP, Dolman JF, Harper JA, et al. Patient-controlled lumbar epidural fentanyl compared with patient-controlled intravenous fentanyl for post-thoracotomy pain. Can J Anaesth 1992;39:214–9.
36. Grant GJ, Zakowski M, Ramanatham S, et al. Thoracic versus lumbar administration of epidural morphine for postoperative analgesia after thoracotomy. Reg Anesth 1993;18:351–5.
37. Ballantyne JC, Carr DB, deFerranti S, et al. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, clinical trials. Anesth Analg 1998;86:598–612.
38. Guinard JP, Mavrocordatos P, Chiolero R, et al. A randomized comparison of intravenous versus lumbar and thoracic epidural fentanyl for analgesia after thoracotomy. Anesthesiology 1992;77:1108–15.
39. Hurford WE, Dutton RP, Alfille PH, et al. Comparison of thoracic and lumbar epidural infusions of bupivacaine and fentanyl for post-thoracotomy analgesia. J Cardiothorac Vasc Anesth 1993;7:521–5.
40. 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.
41. Coe A, Sarginson R, Smith MW, et al. Pain following thoracotomy: a randomized double-blind comparison of

lumbar versus thoracic epidural fentanyl. Anaesthesia 1991; 46:918–21.
42. Silvasti M, Pitkanen M. Patient-controlled epidural analgesia versus continuous epidural analgesia after total knee arthroplasty. Acta Anaesthesiol Scand 2001;45:471–6.
43. Ferrante FM, Lu L, Jamison SB, Datta S. Patient-controlled epidural analgesia: demand dosing. Anesth Analg 1991;73: 547–52.
44. Oka T, Ozawa Y, Ohkubo Y. Thoracic epidural bupivacaine attenuates supraventricular tachyarrhythmias after pulmonary resection. Anesth Analg 2001;93:253–9.
45. Kaiser AM, Zollinger A, De Lorenzi D. Prospective, randomized comparison of extrapleural versus epidural analgesia for postthoracotomy pain. Ann Thorac Surg 1998;66:367–72.
46. Delilkan AE, Lee CK, Yong NK, et al. Post-operative local analgesia for thoracotomy with direct bupivacaine intercostal blocks. Anaesthesia 1973;28:561–7.
47. Toledo-Pereyra LH, DeMeester TR. Prospective randomized evaluation of intrathoracic intercostal nerve block with bupivacaine on postoperative ventilatory function. Ann Thorac Surg 1979;27:203–5.
48. Liu M, Rock P, Grass J. 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.
49. Sabanathan S, Smith PJ, Pradhan GN. Continuous intercostal nerve block for pain relief after thoracotomy. Ann Thorac Surg 1988;46:425–6.
50. Watson DS, Panian S, Kendall V, et al. Pain control after thoracotomy: bupivacaine versus lidocaine in continuous extrapleural intercostal nerve blockade. Ann Thorac Surg 1999;67:825–9.
51. Sabanathan S, Mearns AJ, Bickford Smith PJ, et al. Efficacy of continuous extrapleural intercostal nerve block on postthoracotomy pain and pulmonary mechanics. Br J Surg 1990;77:221–5.
52. Carabine UA, Gilliland H, Johnston JR, et al. Pain relief for thoracotomy. Reg Anesth 1995;20:412–7.
53. Dauphin A, Lubanska-Hubert E, Young JE, et al. Comparative study of continuous extrapleural intercostal nerve block and lumbar epidural morphine in post-thoracotomy pain. Can J Surg 1997;40:431–6.
54. Richardson J, Sabanathan S, Eng J, et al. Continuous intercostal nerve block versus epidural morphine for postthoracotomy analgesia. Ann Thorac Surg 1993;55:377–80.
55. McKenzie AG, Mathe S. Interpleural local anesthesia: anatomical basis for mechanisms of action. Br J Anaesth 1996; 76:297–9.
56. Scheinin B, Lindgren L, Rosenberg PH. Treatment of postthoracotomy pain with intermittent instillations of intrapleural bupivacaine. Acta Anaesthesiol Scan 1989;33:156–9.
57. Kambam JR, Hammon J, Parris WC, et al. Intrapleural analgesia for post-thoracotomy pain and blood levels of bupivacaine following intrapleural injection. Can J Anaesth 1989;36:106–9.
58. Schneider RF, Villamena PC, Harvey J, et al. Lack of efficacy of intrapleural bupivacaine for postoperative analgesia following thoracotomy. Chest 1993;103:414–6.
59. Kreitzer JM, Reuben SS. Central nervous system toxicity in a patient receiving continuous intrapleural bupivacaine. J Clin Anesth 1996;8:666–8.
60. Carretta A, Zannini P, Chiesa G, et al. Efficacy of ketorolac tromethamine and extrapleural intercostal nerve block on post-thoracotomy pain. Int Surg 1996;81:224–8.
61. Singh H, Bossard RF, White PF, et al. Effects of ketorolac versus bupivacaine coadministration during patient-controlled hydromorphone epidural analgesia after thoracotomy procedures. Anesth Analg 1997;84:564–9.
62. Dahl V, Raeder J. Non-opioid postoperative analgesia. Acta Anaesthesiol Scand 2000;44:1191–203.
63. Jain K. Evaluation of intravenous parecoxib for the relief of acute post-surgical pain. Expert Opin Investig Drugs 2000;9: 2717–23.
64. Gupta S, Bhardwaj R, Tyagi P, et al. Anti-inflammatory activity, and pharmacokinetic profile of a new parenteral formulation of nimesulide. Pharmacol Res 1999;39:137–41.
65. Urban MK. COX-2 specific inhibitors offer improved advantages over traditional NSAIDs. Orthopedics 2000;23(Suppl): S761–4.
66. Lefkowith JB. Cyclooxygenase-2 specificity and its clinical implications. Am J Med 1999;106(Suppl):43–50S.
67. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999;282:1929–33.
68. Cannon GW, Caldwell JR, Holt P, et al. Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. Rofecoxib Phase III Protocol 035 Study Group. Arthritis Rheum 2000;43:978–87.
69. Yamamoto T, Sakashita Y, Nozaki-Taguchi N. Anti-allodynic effects of oral COX-2 selective inhibitor on postoperative pain in the rat. Can J Anaesth 2000;47:354–60.
70. Halter F, Tarnawksi AS, Schmassmann A, Peskar BM. Cyclooxygenase 2: implications on maintenance of gastric mucosal integrity and ulcer healing: controversial issues and perspectives. Gut 2001; 49:445–53.
71. Ahmad SR, Kortepeter C, Brinker A, Chen M, et al. Renal failure associated with the use of celecoxib and rofecoxib. Drug Safety 2002;25:537–44.
72. Hawkey CJ. Gastrointenstinal safety of COX-2 specific inhibitors. Gastroenterol Clin North Am 2001;30:921–36.
73. Langman MJ, Jensen DM, Watson DJ, Harper SE, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999;282:1929–33.
74. Bloch MB, Dyer RA, Heijke SA, James MF. Tramadol infusion for postthoracotomy pain relief: a placebo controlled comparison with epidural morphine. Anesth Analg 2002;94: 523–8.
75. Abdel-Ghaffar ME, Abdulatif MA, al-Ghamdi A, et al. Epidural ketamine reduces post-operative epidural PCA consumption of fentanyl/bupivacaine. Can J Anaesth 1998;45: 103–9.
76. Choe H, Choi YS, Kim YH, et al. Epidural morphine plus ketamine for upper abdominal surgery: improved analgesia from preincisional versus postincisional administration. Anesth Analg 1997;84:560–3.
77. Pfenninger EG, Durieux ME, Himmelseher S. Cognitive impairment after small-dose ketamine isomers in comparison to equianalgesic racemic ketamine in human volunteers. Anesthesiology 2002;96:357–66.
78. Chow TK, Penberthy AJ, Goodchild CS. Ketamine as an adjunct to morphine in postthoracotomy analgesia: an unintended N-of-1 study. Anesth Analg 1998;87:1372–4.
79. Cook TM, Riley RH. Analgesia following thoracotomy: a survey of Australian practice. Anaesth Intensive Care 1997; 25:520–4.
80. Karmakar M. Thoracic paravertebral block. Anesthesiology 2001;95:771–80.
81. Richardson J, Sabanathan S, Jones J, et al. 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.
82. Bimston DN, McGee JP, Liptay, et al. Continuous paravertebral extrapleural infusion for post-thoracotomy pain management. Surgery 1999;126:650–6.
83. McKenna RJ, Wolf RK, Brenner M, Fischel RJ, Wurnig P. Is lobectomy by video-assisted thoracic surgery an adequate cancer operation? Ann Thorac Surg 1998;66:1903–8.
84. Lewis RJ, Caccavale RJ, Bocage JP, Widmann MD. Video assisted thoracic surgical non-rib spreading simultaneously stapled lobectomy. Chest 1999;116:1119–24.
85. Kaseda S, Aoki T, Hangai N, Shimizu K. Better pulmonary function and prognosis with video-assisted thoracic surgery than with thoracotomy. Ann Thorac Surg 2000;70:1644–6.

86. Sugiura H, Morikawa T, Sasumura Y, et al. Long-term benefits for the quality of life after video-assisted thoracoscopic lobectomy in patients with lung cancer. Surg Laparosc Endosc Percutan Tech 1999;9:403–8.
87. Petrakis I, Katsamouris A, Drossitis I, et al. Video-assisted thorascopic surgery in the diagnosis, and treatment of chest diseases. Surg Laparos Endosc Percutan Tech 1999;9:409–13.
88. Landreneau RJ, Hazelrigg RS, Mack MJ, et al. Postoperative pain-related morbidity: video-assisted thoracic surgery versus thoracotomy. Ann Thorac Surg 1993;56:1285–9.
89. Nagahiro I, et al. Pulmonary function, postoperative pain, and serum cytokine level after lobectomy: a comparison of VATS and conventional procedure. Ann Thorac Surg 2001; 72:362–5.
90. Miller JD, et al. A randomized controlled trial comparing thoracoscopy and limited thoracotomy for lung biopsy in interstitial lung disease. Ann Thorac Surg 2000;70:1647–50.
91. Scawn N, Pennefather S, Soorae A, Wang J, et al. Ipsilateral shoulder pain after thoracotomy with epidural analgesia: the influence of phrenic nerve infiltration with lidocaine. Anesth Analg 2001;93:260–4.
92. Bucerius J, et al. Pain is significantly reduced by cryoablation therapy in patients with lateral minithoracotomy. Ann Thorac Surg 2000;70:1100–4.
93. Chaplan S. Neuropathic pain: role of voltage-dependent calcium channels. Reg Anesth Pain Med 2000;25:285–95.
94. Omote K, Sonoda H, Kawamata M, et al. Potentiation of antinociceptive effects of morphine by calcium-channel blockers at the level of the spinal cord. Anesthesiology 1993;79:746–52.
95. Jain KK. An evaluation of intrathecal ziconotide for the treatment of chronic pain. Expert Opin Investig Drugs 2000; 9:2403–10.
96. Wang YX, Pettus M, Gao D, et al. Effects of ziconotide, a selective neuronal N-type calcium channel blocker, on mechanical allodynia and heat hyperalgesia in a rat model of postoperative pain. Pain 200;84:151–8.
97. Wang YX, Pettus M, Gao D, et al. Interactions of intrathecally administered ziconotide, a selective blocker of neuronal N-type voltage-sensitive calcium channels with morphine on nociception in rats. Pain 2000;84:271–81.
98. Atanassoff PG, Hartmannsgruber MW, Thrasher J, et al. Ziconotide, a new N-type calcium channel blocker, administered intrathecally for acute postoperative pain. Reg Anesth Pain Med 2000;25:274–278.
99. Lanser P, Gesell S. Pain management: the fifth vital sign. Healthcare Benchmarks 2001;8:68–70.