

Thoracic surgery as a model for postoperative acute and chronic pain

BY CLÉMENT CHASSERY, MD

Pain after thoracotomy is considered particularly intense and prolonged, compared with other types of surgery.¹ The pain is complex because it originates from many different stimuli; there is nociceptive excess carried by somatic and visceral fibres, and a major neuropathic component is added as in all postoperative pain. Moreover, this pain involves several sites: the chest wall, where the surgical incision has been performed; the pleura, particularly, if a thoracic drain is left in place; and the ipsilateral shoulder. Furthermore, thoracic surgery patients often present with reduced functional cardiorespiratory reserves that aggravate the impact of acute post-thoracotomy pain on respiratory and cardiac function. The management of thoracotomy surgical patients is a double challenge, not only because acute pain treatment must be optimal to allow for good short-term rehabilitation, but also to prevent the occurrence of chronic pain.

CHRONICITY OF POST-THORACOTOMY PAIN

According to the IASP (International Association of the Study of Pain), the post-thoracotomy pain syndrome is defined as the recurrence or persistence of pain more than two months after thoracotomy, without any recurrence of the disease. Neuropathic features (eg, sensations of dysesthesia, allodynia, burning) can be found in 35% to 83% of cases. When neuropathic symptoms are present, chronic pain is more severe, tends to last longer, and has a more significant impact on everyday life.² The mechanisms producing chronicity in post-thoracotomy acute pain are complex and incompletely understood. However, intercostal nerve damage associated with a central sensitization phenomenon is usually invoked,^{3,4} even if other mechanisms likely play a role.

The incidence of chronic post-thoracotomy pain following classic intravenous (IV) analgesia reaches 61% at one year.⁵ Depending on studies, the incidence varies between 11% and 80%; this difference is due, notably, to the inhomogeneous definition of chronic post-thoracotomy pain as well as to the diversity of postoperative analgesia regimens (Table 1). In 30% of cases, this chronic pain can last for more than 5 years.⁶ Even though pain intensity is often moderate on a visual analogue scale (VAS 3.3 ± 1.6),⁷ it interferes with everyday life in 50% and sleep in 25% of cases. Furthermore, pain is considered severe in 5% of cases and does not improve over time in > 40% of cases.^{2,5} The main predisposing factors of chronic post-thoracotomy pain are:

- The type or extension of surgery (thoracic wall resection, pleurectomy, pneumonectomy)⁸
- Female gender⁹
- Age < 60 years old⁸
- The intensity and duration of pain during the first postoperative days.^{7,8}

According to some studies, the presence of preoperative pain, postoperative anxiety,^{2,8} and large amounts of postoperative opioids^{5,7} could constitute predisposing factors for chronic pain. Pathophysiologically, the central sensitization phenomenon depends on the quantity of nociceptive impulses received and on the patient's neuronal plasticity, which tends to decrease with age. Therefore, a patient with a less invasive surgery and optimal analgesic treatment, will be at less risk of developing chronic pain.⁴

POST-THORACOTOMY PAIN MANAGEMENT

Surgical approach

Open thoracotomy techniques: The relationship between post-thoracotomy pain at one month and intercostal nerve damage has been well demonstrated.³ Intercostal nerves can be damaged during incision, by surgical retractors, when suturing the chest wall, or after rib resec-

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TABLE 1: Incidence of post-thoracotomy chronic pain

Study (n=) Surgical approach	Type of study	Incidence of chronic pain	Type of postoperative analgesia	Remarks
Dajczman <i>et al.</i> ⁶ (n=56) PLT	Retrospective. Delay of 2 months to 5 years between surgery and survey	54%	Not specified	Chronic pain defined as pain >2 months after surgery without recurrence of disease
Kalso <i>et al.</i> ¹ (n=150) Thoracotomy	Retrospective. Delay of 15 to 48 months between surgery and survey	44%*	– Oxycodone – NSAID – ICB	66% are administered analgesic agents
Pluijms <i>et al.</i> ⁸ (n=149) PLT	Retrospective. Delay of 6 months to 3 years between surgery and survey	52%*	Pre- and postoperative epidural during 48 hours	Chronic pain if >6 months
Maguire <i>et al.</i> ² (n=600) PLT VATS	Retrospective. Delay of 7 months to 7 years between surgery and survey	<1 year: 57% 4-5 years: 36% 6-7 years: 21%	ICB or Parav. or Epidural	
Perttunen <i>et al.</i> ⁵ (n=110) Thoracotomy	Prospective. Survey done at 7 days, 3 months, 6 months, 12 months	3 months: 80%* 6 months: 75% 12 months: 61%	– NSAID – Opioid agents – ICB	
Katz <i>et al.</i> ⁷ (n=23) PLT	Prospective. Survey at 18 months	52%*	PCA morphine <i>iv</i> during 72 hours	Recurrence of disease not researched
Tiippana <i>et al.</i> ⁴¹ (n=111) Thoracotomy	Prospective. Survey at 7 days, 3 months, 6 months	3 months: Epi. 11% PCA 29% 6 months: Epi. 12% PCA 23%	Acetaminophen NSAID Epi. 80% ICB + PCA 20%	Chronic pain defined by VAS >30 moderate or severe

PLT: posterolateral thoracotomy; VATS: video assisted thoracic surgery; PCA: patient controlled analgesia; Epi: thoracic epidural; ICB: intercostal block; Parav: paravertebral block; NSAID: non steroidal anti-inflammatory drug. * Data on chronic pain collected in the study.

tion. Posterolateral thoracotomy with muscle sparing has been presented as a means to minimise intercostal nerve damage compared with standard posterolateral thoracotomy.³ This technique is associated with a decrease in pain and improvement of ipsilateral shoulder mobility during the first seven postoperative days.¹⁰ However, several studies have questioned these results, both in terms of acute pain and of chronic pain at one year.⁹ Similarly, the antero-axillary approach has been proposed as a technique inducing less acute and chronic pain, but this benefit is not found in all studies.¹¹ The technique used to close the chest wall may also play a role in intercostal nerve damage. Taken together, the various surgical techniques used for open thoracotomy seem, nevertheless, to induce similar acute and chronic pain. Two possible explanations can be suggested:

- There are many anatomical variations in the course of the intercostal nerves, thus no surgical technique can guarantee their integrity.
- Surgical retractors, used in all techniques, probably play a major role in damaging the intercostal nerves.

Video-assisted thoracic surgery: Video-assisted thoracic surgery using intercostal trocars allows a decrease in the intensity of pain and a reduction in respiratory impairment during the first 72 postoperative hours.¹² According to some authors, this technique is associated with a decrease in the incidence of chronic pain during the first year following surgery, from 44% to 30%, com-

pared with classic posterolateral thoracotomy.¹³ However, if patient controlled analgesia (PCA) with IV morphine is chosen after video-assisted thoracic surgery, and the results are compared with a posterolateral thoracotomy involving a thoracic epidural with a combination of local anesthetic and opioid agents, the incidence of chronic pain between 3 and 18 months is essentially the same: 36% and 33%, respectively.¹⁴ Video-assisted thoracic surgery provides better acute pain management, but remains disappointing when trying to decrease the incidence of chronic pain. Explanations for these results include the large diameter of the trocars, with the possibility of intercostal nerve injury, and the insertion of the trocars at several levels that can cause damage to several intercostal nerves.

Medical approach

Acetaminophen and anti-inflammatory agents: The efficacy of acetaminophen¹⁵ and non-steroidal anti-inflammatory drugs is well-established for the treatment of ipsilateral shoulder pain that occurs in > 80% of patients after pneumonectomy or lobectomy.¹⁶ This shoulder pain is due to irritation to the mediastinum, diaphragm, and pericardium. Its prevalence appears to be lower in cases of minor thoracic surgery, such as biopsies or wedge resections. The intensity peaks during the first 24 postoperative hours. The pain signal is carried via the phrenic nerve that originates at the C4

level. This explains why thoracic epidurals are ineffective for this type of pain.¹⁶ Phrenic nerve infiltration with a local anesthetic agent applied by the surgeon allows a reduction in the incidence of shoulder pain,¹⁷ but this technique is not recommended because of adverse effects on the respiratory system induced by phrenic nerve paralysis.

After thoracic surgery, administration of non-steroidal anti-inflammatory drugs also allows a 30% reduction in opioid consumption.¹ Ketorolac, administered for 2 to 3 days, does not alter renal function in patients with normal renal function receiving an epidural, despite the mandatory liquid restriction after thoracic surgery.¹⁸ These drugs should nevertheless be avoided in cases of pre-existing renal dysfunction.

Opioid agents: Lipid-soluble opioid agents (eg, fentanyl or sufentanil) or water-soluble agents (eg, morphine), can be administered either by IV PCA or by the intrathecal (IT) or epidural approach. IT sufentanil (15-50 µg) produces analgesia almost immediately, but the duration of effect is limited (3 hr).¹⁹ With IT morphine (0.5 mg) adequate analgesia lasts for 11 hours at rest or 8 hours if coughing, but the intraoperative period may not always be covered.¹⁹ The combination of these two types of compounds thus seems advantageous in order to cover the whole perioperative period. This IT association is associated with a reduction from 84% to 30% in the proportion of patients who will need morphine after surgery. Moreover, when morphine titration is necessary, doses are reduced by a factor of 3 (5 ± 9 mg vs 17 ± 10 mg). Besides, the effective analgesia duration (time during which VAS is > 30) is longer with intrathecal opioid agents (22.7 hr ± 1.6) than with PCA only (16.3 hr ± 5).¹⁹ Limitations of IT injections are:

- limited duration of analgesia (< 24 hr)
- high incidence of acute urinary retention (75% for sufentanil-morphine combination)
- risk of delayed respiratory depression that makes continuous monitoring of the patient during the first 24 hours mandatory.¹⁹

However, despite providing good analgesia, the IT combination of sufentanil and morphine does not provide better spirometry-assessed respiratory function compared with morphine IV PCA. Therefore, administration of IV opioid agents is used when neuraxial regional techniques are contraindicated. This technique is also useful in the treatment of shoulder pain that is refractory to acetaminophen and non-steroidal anti-inflammatory drugs. It is also indicated to supplement an inadequate continuous regional technique or to prevent withdrawal symptoms in patients who were administered opioid agents chronically before surgery. With PCA, morphine (or hydromorphone PCA in cases of renal failure) is most often prescribed. As soon as efficient bowel function resumes, early switching to an oral agent is preferred to facilitate patient mobilization.

Ketamine: After conventional posterolateral thoracotomy, intravenous ketamine (0.05 mg/kg/hr; about 3 mg/hr) postoperatively for 72 hours potentiates the effects of a thoracic epidural combining ropivacaine (0.15%) and morphine (0.05 mg/mL) without any notable side effects.²⁰ Ketamine decreases pain at 1 and

3 months, and improves physical activity at one month. At this dosage, it is not effective on pain at 6 months or on incisional hyperalgesia phenomena.²⁰ In order to reduce hyperalgesia, the recommended dosage for major surgery is 0.5 mg/kg/hr during surgery (either continuous, or as repeated boluses every 30 minutes) and then one quarter of the dose for 24 hr, and finally one eighth of the dose for another 24 hours.²¹ Furthermore, ketamine, when combined with a thoracic epidural, has been shown to be effective in preventing chronic pain at one year following major gastrointestinal surgery, at a dose of 0.5 mg/kg before incision and 0.25 mg/kg/hr until closure.²²

Gabapentin and pregabalin: Gabapentin, first marketed in the nineties for its antiepileptic properties, is known to be effective in treating chronic neuropathic pain, complex regional pain syndromes, and restless legs syndrome. Gabapentin is believed to act on a specific receptor, the alpha 2 delta subunit of presynaptic type N voltage-dependent calcium channels, which are overexpressed in the dorsal horn of the spinal cord and in spinal ganglia in cases of neurological injury. The advantages of gabapentin are that it does not interact with hemostasis and does not induce respiratory depression. Further, its anxiolytic properties can be useful preoperatively. Recommended dosages are 300 to 3200 mg/day in 2-3 doses. Bioavailability of gabapentin is 36% to 60% and decreases with the ingested dose because of a saturable absorption at the small intestine level. Gabapentin is not metabolized and is eliminated in the urine, therefore, dosages should be modified in renal failure. Side effects are rare and usually mild: dizziness, vertigo, headaches, nausea, vomiting, and ataxia. Its perioperative administration has been the subject of a recent meta-analysis focusing on 16 studies in gynecologic, orthopedic, spinal, and abdominal surgeries.²³ Despite a higher sedation risk, gabapentin is associated with reduced pain scores and morphine consumption in the first 24 hours.

Combined with an epidural for lower limb surgery, the following results were observed with gabapentin: less pain in the first 16 hours, reduced epidural drug administration over 72 hours, and increased patient satisfaction despite a feeling of dizziness in 35% of patients.²⁴ A recent study showed that the administration of gabapentin at a dose of 400 mg q6 hr for 5 days is associated with a reduction in the incidence and intensity of pain at one month as well as a decrease in the consumption of analgesic agents at one month after abdominal hysterectomy.²⁵

Gabapentin is effective in the treatment of chronic pain after thoracic surgery with a decrease in paresthesia around the wound in 75% of cases. Moreover, only 6.7% of patients discontinued treatment because of side effects and 88.9% reported that they were satisfied.²⁶ It appears that gabapentin provides better postoperative pain scores, shows minimal side effects, and may improve patient outcome in the long term. However, other randomized prospective studies on larger patient cohorts will be necessary to confirm these preliminary results.

Pregabalin is a more recent compound related to gabapentin that acts on the same receptors. Interest in

this agent is primarily due to its 90% fixed bioavailability, independent of dose. Like gabapentin, this compound is not metabolized and is eliminated unchanged in urine. In Canada, pregabalin is indicated for neuropathic pain related to diabetes or postherpetic pain. The recommended dosage is 150 to 600 mg, 2-3 times a day. Its main side effects are vertigo (3.3%), dizziness (4.8%), nausea (3.7%), headaches (1.1%), drowsiness (1.8%), and peripheral edema (1.5%).²⁷ Pregabalin has not been well-studied in surgical patients.

Regional anesthesia

Thoracic epidural: A thoracic epidural is considered the gold standard for providing analgesia after open thoracotomy.²⁸ It decreases postoperative respiratory complications and reduces to 21% the incidence of post-thoracotomy chronic pain at one year.⁹ It can be indicated for video-assisted thoracic surgery if the risk of transformation into open thoracotomy is significant and if the patient's respiratory function is severely impaired. Ideally, the tip of the epidural catheter should be located at the level involved with the surgical incision. Puncture is thus traditionally performed between T6 and T8.²⁸

The injection into the epidural catheter before the surgical incision decreases pain scores while coughing at 24 and 48 postoperative hours, but it does not affect pain scores at rest. This benefit is small because pain scores are, in any case, less than 3/10, which is the generally accepted criterion to describe adequate pain control.²⁹ Furthermore, this benefit is accompanied by intraoperative hemodynamic consequences that must be weighed against the analgesic benefit in the most fragile patients.⁹ The incidence of chronic pain at 6 months appears similar, whether the epidural injection is performed before or after the surgical incision.²⁹ Ideally, the epidural should be used until the removal of thoracic drains (ie, 4-5 days postsurgery). The anesthetic solution can be administered either continuously at 0.1 mL/kg/hr, adjusted to clinical efficacy, or by patient controlled epidural administration (PCEA) at a background rate of 4-6 mL/hr plus boluses of 2-4 mL/10 min.²⁸

Generally, the type of solution used in a thoracic epidural is a combination of a long-duration local anesthetic agent (bupivacaine or ropivacaine) with a lipid-soluble opioid agent (fentanyl or sufentanil). This combination is the best compromise between the adverse hemodynamic effects of local anesthetics and the side effects of opioid agents (sedation, pruritus, nausea, respiratory depression, etc.). The type of local anesthetic is of little importance as long as equianalgesic concentrations are used. Accordingly, bupivacaine 0.1% or ropivacaine 0.15% combined with fentanyl 5 µg/mL have the same efficacy when administered epidurally after posterolateral thoracotomy. Moreover, these two combinations are better than ropivacaine 0.2% on pain during effort.³⁰

The optimal concentration of fentanyl combined with bupivacaine 0.1% is probably 5 µg/mL. Lower fentanyl concentrations require an increase in infusion rates and do not provide adequate analgesia. Higher concentrations (10 to 20 µg/mL) are associated with an increase in side effects (eg, pruritus or sedation) without improving analgesia.³¹

The addition of epinephrine, at a concentration ≥ 1.5 µg/mL, to a solution of bupivacaine 0.1% and fentanyl 2 µg/mL in the thoracic epidural, results in better pain scores, especially when coughing, and decreases the incidence of pruritus after thoracic or abdominal surgery.³² The mechanism of action of epinephrine in this setting is a reduction in the systemic absorption of local anesthetic agents and fentanyl at the epidural level and, possibly, in an action on the spinal cord dorsal horn alpha 2 adrenergic receptors.³² Concerns about spinal cord blood flow following the use of epinephrine are unfounded in concentrations generally used in humans.

The risk of permanent neurological damage related to thoracic epidural is estimated at 0.07% only. However, the various contraindications should be observed and this procedure should be performed on a conscious and cooperative patient.³³

Paravertebral block: A paravertebral block can be performed at one or several levels, either by a single injection, or continuously with a catheter. This block is performed percutaneously by the anesthesiologist or by the surgeon, using an endothoracic approach. In the latter case, the technique is called "intercostal block by extrapleural approach." The paravertebral block produces an ipsilateral block of the intercostal nerves and of the sympathetic ganglionic chain. Epidural diffusion is believed to be present in 70% of cases after a percutaneous technique, but the anesthetic solution volume in the epidural space is thought to be too low to have any clinical effect.³⁴ The technique involving only one puncture point can produce anesthesia that extends over 5 dermatomes, if an adequate volume of anesthetic solution is used (approximately 0.3 mL/kg).

Compared with PCA, paravertebral block, if performed by a single injection after video-assisted thoracic surgery with 0.4 mL/kg of 0.375% bupivacaine with epinephrine, is associated with better pain control at rest and with coughing in the first 48 hr.³⁵ Multiple and multilevel injections of 5 mL bupivacaine (0.5%) with epinephrine over 6 levels results in a good spread of the local anesthetic agent, but appears to shorten the duration of analgesia to only 6 hours.³⁶ A recent meta-analysis comparing paravertebral block to thoracic epidural after thoracotomy found that the quality of analgesia was identical for 48 postoperative hours, but that the side effects (hypotension, nausea, vomiting, acute urinary retention) as well as, pulmonary complications and failure were less frequent in the paravertebral group.³⁷ In addition, a paravertebral block could play a role in preventing chronic pain.³⁴ The results of these studies support the

notion of using a paravertebral block after thoracotomy as first-line treatment similar to a thoracic epidural and, perhaps, even more so because the technique seems easy to learn and presents a failure rate of < 10%.³⁴ This block can also be considered a safer alternative than a thoracic epidural in cases of suspected septic state or moderate hemostasis disorders.³⁴ In this case, the risk/benefit ratio of the technique should be clearly discussed with the patient. The major complications and their frequency are evaluated at 3.8% for vascular puncture, 4.6% for hypotension (by vagal mechanism or hypovolemia), 1.1% for pleural puncture, and 0.5% for pneumothorax.³⁴

Intrapleural injection of local anesthetic agents: Intrapleural injection of 20 mL bupivacaine (0.5%) every 4 hours after thoracotomy is not better than saline for pain scores and postoperative opioid consumption. Moreover, in the group receiving bupivacaine, two patients out of 40 described neurological symptoms of systemic toxicity to local anesthetic agents after the injection. The lack of efficacy and the risks of toxicity make the intrapleural injection of local anesthetic agents obsolete and it should no longer be performed.³⁸

Intercostal block: The intercostal block can be performed either by the anesthesiologist using a percutaneous approach or by the surgeon using an internal approach. Generally, multiple injections of 2-3 mL bupivacaine (0.5%) with epinephrine are done at multiple levels. This technique is superior to opioid agents administered by systemic approach for the management of postoperative pain. Even though the duration of analgesia is limited to < 24 hours with a single injection, the intercostal block seems to be effective over several days. The block can be performed pre- or postoperatively, without affecting its effectiveness. The estimated risk of pneumothorax is 0.07%, recognizing that an indication for drain placement is common in thoracic surgery. Furthermore, no cases of systemic toxicity were reported in a cohort of 11,000 patients.³⁹ The insertion of a catheter close to the intercostal nerve has been described, but this provides poorer analgesia compared with thoracic epidural and can induce osteomyelitis.⁴⁰ Finally, unlike a thoracic epidural, an intercostal block does not appear to reduce respiratory complications. This technique should therefore not be offered as a first choice after thoracotomy.

This is the reason why some authors recommend the intercostal block by extrapleural approach; a catheter is inserted under the parietal pleura by the surgeon using an endothoracic approach and maintained with 0.1 mL/kg/hr local anesthetic agent. Continuous block of intercostal nerves at several levels is thus obtained if the parietal pleura are intact and can serve as a reservoir. This technique, which is similar to a paravertebral

block when considering the spread of local anesthetic, is superior to opioid agents administered systemically and equal to thoracic epidural for pain management.³⁹ However, even though few cases of systemic toxicity to bupivacaine have been reported, plasma levels can approach 5 µg/mL at 48 hr.³⁴ In terms of complications related to the extrapleural approach, 3 cases of toxicity to local anesthetic agents, 1 case of osteomyelitis, 1 case of Horner's oculopupillary syndrome, and one transient hypotension have been reported among 383 patients.³⁹

CONCLUSION

Post-thoracotomy chronic pain occurs frequently and, without prevention, affects more than 50% of patients. This type of chronic pain has significant repercussions on the quality of life for patients and important social costs. Adapting a multimodal perioperative strategy can prevent pain, particularly, less invasive surgery and efficient analgesia achieved with a thoracic epidural or paravertebral catheter. Even though ketamine seems to provide additional benefits in the acute and chronic phases, its optimal dosage has yet to be determined. Finally, gabapentin and pregabalin appear promising in the prevention of chronic pain thanks to their pharmacological properties; however, their role in thoracic surgery should be defined by further studies.

POINTS TO REMEMBER:

- Chronic pain after thoracotomy is defined as a pain persisting for more than 2 months after surgery.
- Chronic pain affects more than 50% of patients after thoracotomy and the neuropathic features of the pain are significant.
- The mechanisms producing acute chronic pain post-thoracotomy are associated with intercostal nerve damage and sensitization of the central nervous system.
- A careful management strategy of anesthesia for patients after thoracotomy should be planned in order to prevent the development of chronic pain.
- A thoracic epidural associated with a local anesthetic and a lipid-soluble opioid, as well as a paravertebral catheter remain the chosen techniques for treating acute post-thoracotomy pain and preventing pain chronicity.
- Video-assisted thoracic surgery allows a reduction in the intensity of acute postoperative pain, but it does not reduce the incidence of chronic pain.

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