Postoperative analgesia after pulmonary resection with a focus on video-assisted thoracoscopic surgery

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Summary

Video-assisted thoracoscopic surgery is a widespread technique that has been linked to improved postoperative respiratory function, reduced hospital length of stay and a higher level of tolerability for the patients. Acute postoperative pain is of considerable significance, and the late development of neuropathic pain syndrome is also an issue. As anaesthesiologists, we have investigated the available evidence to optimize postoperative pain management. An opioid-sparing multimodal approach is highly recommended. Loco-regional techniques such as the thoracic epidural and peripheral blocks can be performed. Several adjuvants have been employed with varying degrees of success both intravenously and in combination with local anesthetics. Opioids with different pharmacodynamic and pharmacokinetic profiles can be used, either through continuous infusion or on demand. Non-opioid analgesics are also beneficial. Finally, perioperative gabapentinoids may be implemented to prevent the onset of chronic neuropathic pain.

Keywords: Video-assisted thoracoscopic surgery • Postoperative analgesia • Acute postoperative pain • Chronic pain syndromes • Thoracic epidural • Loco-regional anaesthesia

INTRODUCTION

Video-assisted thoracoscopic surgery (VATS) is a renowned technique that has been linked to improved postoperative respiratory function [1], reduced hospital length of stay and a higher level of tolerability for the patients [2]. The pathophysiology of pain after VATS does not differ much from that following thoracotomy as it is mostly due to the surgical incision and the local trauma, the presence of a chest tube and the shoulder pain syndrome [3]. In general, both inflammatory response and noxious stimuli appear less relevant with such an approach [4]. Nevertheless, acute postoperative pain, especially after major procedures like lobectomies, is still moderate to severe [5]. The general idea is that the analgesic requirements of VATS are considerable but not high enough to justify the side effects of the measures required after an open thoracotomy. Unfortunately, most of the available evidence does not deal specifically with VATS and much of the information needs to be deduced from studies conducted on open thoracotomies. Moreover, various subtypes of VATS exist (uniportal, multiportal and robotic) with possible implications on postoperative pain, but this is beyond the scope of our review. Regardless of the surgical approach, an adequate pain management throughout the perioperative period remains paramount to improve respiratory dynamics, reduce collateral effects and lower the insurgence of chronic pain [6].

The most commonly used drugs for this goal are the opioids. However, they exhibit numerous adverse effects such as respiratory depression, postoperative nausea and vomiting (PONV) and tolerance development, without considering their possible role in tumour recurrence as hypothesized by laboratory studies [7]. Considering the comorbidities of the majority of patients eligible for thoracic surgery, it is mandatory to limit their use [8]. A multimodal analgesic approach should be preferred.

LOCO-REGIONAL ANALGESIA

Thoracic epidural analgesia

Until very recently, the scientific research on loco-regional analgesia for lung surgery has focused on the thoracotomic approach because of its greater popularity. Within this context, thoracic epidural analgesia (TEA) has demonstrated great results both in terms of intraoperative and postoperative pain control and in terms of patient outcome [9, 10]. Its use is recommended by the Italian guidelines for the first 48–72 h [11]. To improve patient satisfaction and limit overdosage, devices for on-demand administration of local anaesthetics in the epidural space have been developed. Compared with the continuous infusion, patient-controlled epidural analgesia has proved slightly less effective for

pain control but with reduced incidence of adverse effects such as vomiting and motor block [10].

The peripheral blocks

The paravertebral block (PVB) has gained popularity in more recent times. Pneumothorax, the main risk associated with its performance, does not represent an issue in thoracic surgery, considering that the placement of a drain tube is already expected. The PVB can be accomplished by the single-shot infiltration or by placing a catheter. The continuous infusion in the postoperative period appears to offer more durable effects, at least after thoracotomy [12], and typically lasts several days [13]. The best local anaesthetic and its optimal posology still need to be identified. Common regimens include bupivacaine 0.1% at 5–12 ml/h or 0.25% at 0.1 ml/kg/h and ropivacaine 0.2% at 4 ml/h [14].

The intercostal nerve block can be performed by the anaesthesiologist or the surgeon under direct view, and it is indicated whenever TEA or PVB cannot be accomplished [9]. After VATS procedures, the single-shot technique is effective for the first 16 h, and opioid consumption is lower for the first 24 h [15]. The placement of a catheter for postoperative infusion is also possible, and it has proved comparable to TEA in terms of postoperative pain control up until the 5th day following thoracotomy [16].

The serratus anterior plane block is a brand-new block of the thoracic wall that has been described for the first time in 2013 [17]. It affects the area innervated by the T2–T9 spinal roots, and it lasts an average of 12.5 h. An advantage of this technique is the sparing of the sympathetic nerves resulting in improved haemodynamic stability. For these reasons, the serratus anterior plane block has been used as an alternative to TEA, achieving not only a reduced incidence of hypotension but also lower pain scores, despite comparable morphine consumption, and no significant side effects [18]. Such results have been obtained with levobupivacaine 0.25% (30 ml) for the initial bolus and a continuous infusion of 0.125% (5 ml/h). The serratus anterior plane block has also been described as a rescue strategy in case of epidural failure [19].

The phrenic nerve block has also been recently described [20], but its effect on respiratory mechanics has not been sufficiently evaluated. We do not feel it should be recommended yet.

Thoracic epidural analgesia versus the paravertebral block

Some authors indicate TEA as the gold standard for thoracic surgery [21], whereas for others both TEA and PVB should be considered as reference [5]. No differences in terms of 30-day mortality, major cardiorespiratory or neurological complications and length of stay have been reported after thoracotomic procedures [22]. The possibility to associate opioids with local anaesthetics is one of the advantages of the epidural, while it is not recommended with the PVB. This may offer a superior pain control and better spirometric parameters to both the PVB and TEA with no opioid [23]. Adverse effects such as hypotension, PONV and urinary retention are rare but feared complications of TEA, adding to the rising popularity of the PVB [8]. Another advantage of the PVB with respect to TEA seems to be the lower failure rate [24].

Loco-regional analgesia after video-assisted thoracoscopic surgery

For thoracoscopic surgery, a consensus on the best approach for pain control has not been reached [25]. TEA has not proved superior to intravenous patient-controlled analgesia (PCA), except maybe for patients with pre-existent tolerance to opioids or when a thoracotomic conversion is foreseeable [15]. On the other hand, the evidence to support this argument is scarce and very heterogeneous, especially for lobectomies [5].

The role of other loco-regional techniques is extremely promising, although it requires further investigation. The PVB seems to offer effective pain control after VATS; given its safety profile and the possibility to be performed by the surgeon under direct view, it is advisable that this analgesic technique be used more frequently. It could assume a central role for fast-track programmes in thoracic surgery [26].

The benefit of extending the effects of the PVB with a catheter for postoperative infusion has not been adequately studied. The single-shot infusion has already shown a prolonged efficacy in reducing opioid consumption when compared with the placebo [27, 28]. Similarly, the analgesic effect of extemporary PVB has proved superior to the infiltration of the surgical wound for up to 24 h [29].

Adjuvants

Clonidine. Reported epidural doses are especially heterogeneous, varying from 75 μg to 800 μg for the bolus and from 0.3 μg/kg/h to 2 μg/kg/h for the infusion [30]. Following open procedures, the continuous infusion in the epidural space seems to improve both static and dynamic pain but at the expense of increased incidence of sedation and hypotension [31]. On the other hand, adding just 2 μg/kg clonidine to the initial bolus has not shown significant side effects [32], and it could be of use in patients at risk for opioid-induced hypoventilation. In conclusion, the evidence is not strong enough to recommend a routine use [33].

Dexmedetomidine. The combined epidural use of bupivacaine and dexmedetomidine has shown better pain control both intraoperatively and postoperatively and reduced opioid consumption [31]. The effectiveness of adding dexmedetomidine for TEA has been confirmed in a meta-analysis and it has been proposed for the PVB as well [34]. However, it is not supported by any guidelines, and it is still off-label in many countries.

Magnesium. The epidural administration of magnesium with bupivacaine seems to reduce the incidence of postoperative shivering and the demand for rescue doses of analgesics [32].

Dexamethasone. The epidural use of dexamethasone has been investigated only recently. Its efficacy has not been determined univocally, but it could still have a role as an adjuvant [35]. On the other hand, rare but extreme adverse reactions have been described after the injection of steroids in the epidural space, including sight loss, cerebral ischaemia, paralysis and death [36].

Epinephrine. Its application in neuraxial analgesia is well established, for both the direct effect on spinal α-adrenergic

receptors and the induced vasoconstriction resulting in slower drug clearance. It has demonstrated benefits in terms of quality and duration of TEA with local anaesthetics and opioids [37]. The minimum effective concentration after major procedures has been found around 1.5 μg/ml [38]. No detrimental effects on the spinal cord have been reported in animal studies with doses up to 200 μg [39].

Ketamine. The epidural combination of ketamine with opioids and/or local anaesthetics seems to be effective in providing relief from postoperative pain, reducing the total demand of opioids without increasing the incidence of PONV or psychomimetic events. It has been suggested that the epidural administration has the same efficacy as the intravenous route in preventing the development of hyperalgesia at the surgical wound [40].

The current guidelines still do not recommend epidural use of adjuvants such as magnesium, ketamine, benzodiazepines, neostigmine and tramadol due to insufficient evidence on their potential benefits and safety limits. Moreover, the majority of these medications are often available only in solutions with preservatives that could display neurotoxic properties [33].

OPIOIDS

The exclusive administration of opioids seems to be effective in controlling the persistent component of pain but not the episodic type associated with cough and movement. This would require higher plasmatic levels of these drugs and the resulting side effects of sedation and hypoventilation. The clinical problem of this pharmacological class is linked to its narrow therapeutic window.

The endovenous use of opioids can be obtained by the continuous infusion or on demand through dedicated devices (PCA). A proper loading dose has to be administered to reach therapeutical plasmatic concentrations, especially when PCA is employed. The continuous infusion guarantees a good level of analgesia but is often associated with overdosing.This inconvenience has led to increased PCA use over the years. The 2 techniques were initially reported equipotent in terms of pain control [10], but the development of more sophisticated devices has allowed PCA to gain in popularity. Nowadays, the continuous infusion is considered outdated and does not find application in the scientific literature over the last 5 years. A major drawback of PCA is its restriction to patients with an adequate cognitive function and thus capable of understanding its operation and safety limits. The importance of instructing patients during the preoperative phase should not be underestimated.

PCA does not seem to be effective for dynamic pain [9]. The combination of a basal infusion and on-demand supplementary doses has been proposed to minimize pain fluctuations during the first hours [41] but has resulted in more collateral effects than effective benefits [33]. Others have suggested the coadministration of opioids with different pharmacokinetic profiles: a successful example is the combined use of remifentanil and morphine [42].

Finally, it must be emphasized that the administration of opioids in the preoperative phase with the purpose of reducing their postoperative use is no longer recommended [43].

Strong opioids

Morphine still represents the opioid of reference, but the recommended dosages found in the literature are particularly heterogeneous. For PCA, the bolus on demand usually consists of 0.5–3 mg, with lockout times of 3–15 min.

Oxycodone is commonly used when oral intake is resumed. It is often administered in association with naloxone, but after VATS, controlled-release formulations of the sole drug seem to be more effective for both static and dynamic pain [44]. The suggested dose is 10 mg every 12 h after the interruption of morphine. An equianalgesic conversion table should be consulted when switching from a previous opioid. In most charts, a ratio of 20 mg of oral oxycodone per 30–40 mg of oral morphine is reported, but when parenteral morphine is used, the calculated ratio is in fact 1.5–2:1. It is best to start with a daily regimen of 75% equivalence, provide rescue doses of 5–15% and closely monitor the clinical response to tailor therapy according to patient requirements [45].

Sufentanil is preferred in many centres for the higher bioavailability. The sufentanil sublingual tablet system is a new form of PCA with interesting features [46]. The proposed dosage is 15 μg per tablet, with a lockout time of 20 min. When compared with morphine-based PCA, it is associated with a more rapid analgesia and higher success rates according to both patients and health care personnel. It is generally well tolerated, avoids programming mistakes and imposes less restriction on postoperative mobilization. Collateral events are comparable, and desaturation is even less common. The sufentanil sublingual tablet system represents an appealing alternative after major abdominal procedures and knee surgery [47]. Its use in thoracic surgery has not been reported.

Weak opioids

Codeine is a weak opioid whose analgesic activity depends on its metabolism to morphine. It is often commercialized in association with non-opioid analgesics. The combination seems to possess higher analgesic potency and prolonged clinical effect than the single components [48]. The recommended posology *per os* is 30 mg with paracetamol 500 mg every 4 h. Despite its widespread use, no reports on thoracic surgery are available.

Dihydrocodeine is a semisynthetic derivative with a similar activity. In many countries, it is only available as cough syrup or droplets and will not be discussed further.

Tramadol is another weak opioid that exploits other mechanisms of action, such as the inhibition of serotonin and norepinephrine reuptake. When used as a sole drug, it does not provide adequate relief after moderately painful surgery [49]. Moreover, the concurrent use of serotonin receptor antagonists such as ondansetron may reduce its analgesic potency [50]. Adverse effects are minor when compared with the other opioids. The risk of respiratory depression in particular is almost insignificant, and the hypoxic ventilatory response is not compromised [51], except in case of chronic renal failure [52]. It can induce mental confusion and hallucinations in the elderly or seizures if concurrent risk factors are present. Postoperative use of tramadol is recommended only after the major opioids have been suspended. The recommended posology is 50–100 mg *per os* or intravenously every 6 h.

NON-OPIOID ANALGESICS

Paracetamol

The oral formulation is widely used both as an analgesic and for its antipyretic properties. It neither causes respiratory

complications nor side effects typical of non-steroidal anti-inflammatory drugs (NSAIDs). The potential hepatotoxicity is a disadvantage. It is often used to reduce opioid requirements in the postoperative period or after a variety of medical interventions [53]. Its administration in critical patients has shortened extubation times [54] and reduced early shoulder pain after thoracotomy [55]. Given its safety profile and the synergism when used in combination with other drugs, paracetamol should be introduced in multimodal analgesia as a first-choice drug.

When switching from parenteral to oral therapy, orosoluble and orodispersible solutions should be used for faster response times, with values in the therapeutic interval after only 15 min [56].

Non-steroidal anti-inflammatory drugs

The clinical activity of NSAIDs is based on the inhibition of cyclooxygenase (COX) and thus of prostaglandin synthesis. Their use as a postoperative analgesia reduces opioid requirement by 30–35%. In thoracic surgery, there is some evidence with indomethacin. Furthermore, the combination with paracetamol has shown synergistic properties [57].

The use of NSAIDs is limited by their side effects, such as inhibition of platelets aggregation, impairment of renovascular autoregulation and irritation of the gastric mucosa. Selective inhibitors of the COX-2 isoform, expressed prominently during inflammatory states, were developed to limit such adverse events. Indeed, better pain control has been reported with celecoxib with no significant effect on coagulation. An increased risk of cardiovascular and cerebrovascular events has been shown from a pharmacovigilence point of view, yet the American guidelines still consider their administration in patients with no contraindications (e.g. celecoxib 200–400 mg before surgery) [33].

Side effects aside, the most effective (and the most cited in the scientific literature) NSAID is intravenous ketorolac. Its administration has led to a 36% reduction in postoperative morphine demand without any difference in the rate of complications [58]. Its use is not associated with an increased risk of bleeding after major abdominal, neuro or orthopaedic surgery, while no such evidence is available for thoracic surgery [59]. The recommended posology is 15–30 mg intravenously every 8 h for 2 days. Recent studies demonstrate the same analgesic effect between the doses of 10, 15 and 30 mg [60].

Ketamine

Ketamine has long been administered to reduce opioid requirements and is recommended whenever contraindications to locoregional analgesia exist [9]. It is used for its ability to induce hypnosis while preserving the ventilatory drive, but it also exhibits analgesic properties, even at low concentrations. It improves pain control, regardless of the timing, the route of administration and the posology of the associated opioid [61]. It represents an option especially in cases a pre-existing opioid addiction [33].

Among the side effects, dysphoria has been reported, although its incidence is reduced when ketamine is used at an analgesic dose of 0.5–1 mg/kg (or under 10 mg/h in infusion) [62].

α_2-Agonists

Adrenergic pathways seem to play an important role in the modulation of pain. The main target of α_2-agonists is likely located in the gelatinous substance of the spinal dorsal horns where α_2 receptors are particularly represented. Despite their sedative effects, α_2-agonists do not affect the respiratory drive. A single dose of clonidine 3 μg/kg before induction has proved to reduce opioid consumption for 24 h after thoracotomy [63].

Dexmedetomidine is a more selective α_2-agonist used in the continuous infusion. It appears beneficial after thoracotomy, as shown by the decreased need of rescue doses by both the epidural [41] and the intravenous routes [64]. After VATS, PCA with dexmedetomidine and oxycodone reduces opioid consumption and improves patient comfort with fewer episodes of PONV [65]. Furthermore, dexmedetomidine antagonizes opioid-related muscular stiffness and postoperative shivering [66]. Its limits are represented by bradycardia and hypotension: its use must be carefully evaluated in patients already on beta-blockers, on fluid-restriction, or at increased risk of hypotension because of epidural-induced sympathetic depression. In any case, the use of dexmedetomidine must be accurately titrated to avoid haemodynamic compromise [9].

Dexamethasone

In the perioperative phase, it not only reduces PONV but also improves analgesia. A single administration is associated with better pain control, reduced opioid consumption and less need for rescue medications. No difference between the doses of 4 and 8 mg has been observed. Increases in glycaemia have been reported as side effects, yet without clinical consequences such as infections or delays in wound healing [67].

Nefopam, flupirtine and other centrally acting non-opioid analgesics have not been discussed here due to a lack of evidence in the field of thoracic surgery and doubts about their safety profiles.

NEUROPATHIC PAIN

A separate discussion is required for neuropathic pain and its propensity to develop in the long term after thoracic surgery. It is caused by the direct or indirect damage to the somatosensory system and is characterized by a distinctive dermatomic distribution and features such as spontaneous reactivations, allodynia and dysaesthesia [68]. The chronic form that develops after thoracic surgery is known as post-thoracotomic pain syndrome (PTPS) and is diagnosed when the pain recurs or persists for more than 2 months after the procedure. Its prevalence is extremely variable in the various reports, possibly because of an ambiguous definition, an inadequate follow-up or imprecise data collection. In any case, it appears to be a relevant phenomenon, as it brings a significant and debilitating discomfort to patients [69].

Although still incompletely understood, it is speculated that PTPS evolves from an acute damage to the afferent nerves of pleura, diaphragm or rib cage. The insult is often generated by the intraoperative lesion of an intercostal nerve, the placement of trocars, the traction of the ribs or by the surgical incision itself. The pre-existence of some form of chronic pain and a low level of confidence in the good outcome of surgery also seem to favour the development of the syndrome [70]. The lack of knowledge of its precise pathophysiology prevents the identification of patients at higher risk and the implementation of preventative therapy.

Table 1: A simplified scheme for multimodal analgesia after VATS

Locoregional analgesia	Systemic opioids	Other analgesics
Single-shot techniques **PVB/ICNB** can be performed by surgeon less hemodynamic compromise **SAPB** needs to be US-guided also as rescue strategy	**Major opioids** **IV Morphine** PCA with no basal infusion with repeatable boli of 0.5-3 mg suggested lockout time of 3-15 min and proper intraoperative loading dose **Oral oxycodone** 10 mg *per os* bid or calculated equianalgesic dose if switching from IV opioid **Sublingual sufentanil** no evidence available for thoracic surgery	**Paracetamol** 1 g qid (or 15 mg/kg if BW < 50 kg or liver disease) **NSAIDs** e.g. ketorolac 15-30 mg tid **Dexamethasone** 4-8 mg intraoperative bolus also for prevention of PONV
Continuous infusions *(To be considered if long procedure or possible conversion to thoracotomy)* **Thoracic epidural (TEA)** can also be used with opioids **Peripheral block + catheter**		**Ketamine/dexmedetomidine** only under surveillance (e.g. PACU) for side effects
	Minor opioids no clear indication only after suspension of major opioids	**Gabapentinoids** no clear evidence for prevention of PTPS

bid: *bis in die* (twice daily); BW: body weight; ICNB: the intercostal nerve block; IV: intravenous; NSAIDS: non-steroidal anti-inflammatory drugs; PACU: post-anaesthesia care unit; PCA: patient-controlled analgesia; PONV: postoperative nausea and vomiting; PTPS: post-thoracotomic pain syndrome; PVB: paravertebral block; qid: *quarter in die* (4 times a day); SAPB: serratus anterior plane block; TEA: thoracic epidural analgesia; tid: *ter in die* (thrice daily).

Intravenous ketamine has not shown protective effects [71]. Currently, the best approach consists in the complete block of all nociceptive afferences for the period that extends from the surgical incision to the healing of the wound. An inadequate treatment for perioperative pain increases the risk of developing PTPS [6, 9]. Systematic reviews encourage the adoption of locoregional techniques: TEA seems to be effective in the prevention of PTPS. More studies are required to evaluate the efficacy of blocks such as the PVB [72].

The choice of the surgical technique also seems to play a crucial role in the genesis of the chronic pain [9], although an optimal approach has not been identified. Different accesses and muscle-sparing techniques have not shown consistent results in terms of prevention. VATS appears to be less associated with PTPS when compared with thoracotomy [73], but this has not been adequately confirmed.

Not all patients who develop PTPS require chronic antalgic therapy [69]. The pharmacological class of choice is represented by the gabapentinoids, whereas the chronic use of opioids is no longer recommended.

Gabapentin

It is a highly tolerated and safe drug regularly used for postherpetic neuralgia and chronic neuropathic pain, whose most commonly reported side effects include vertigo and sleepiness. Various studies have demonstrated that only high doses (1200–1400 mg) of gabapentin reduce opioid use after general surgery [74]. For chronic neuropathic pain after thoracic surgery, gabapentin has been confirmed as a safe, well-tolerated drug with few side effects even at high doses [75]. Its effectiveness in the preoperative period is however, low: 600 mg before surgery did not reduced pain scores, opioid consumption or the incidence of pain at 3 months [69]. A single dose did not seem to be beneficial, whereas the continued administration of high doses of gabapentin in the postoperative period could be of use in the control of both acute and chronic pain [76].

Pregabalin

Pregabalin, commonly used for both central and peripheral neuropathic pain, has been proved safe and effective in reducing perioperative consumption of opioids after thoracic surgery, with visual disturbances as the sole side effect. Its favourable pharmacokinetics with respect to gabapentin (bioavailability of 90% and 33–66%, respectively) allows the administration of lower doses, with reduced collateral effects. The literature on the subject is scant: 150 mg before surgery and for the first 21 postoperative days has shown to reduce the incidence of neuropathic pain after posterolateral thoracotomy [77]. In patients with unsatisfactory pain control, its administration has brought about an improvement in analgesia and a decrease in the incidence of pain at 3 months [78].

The literature about the PTPS and the specific preventive therapies is very limited, particularly for VATS. Thus, special consideration is required when developing fast-track protocols, not only to ensure adequate postoperative analgesia during the hospital stay but also to monitor the quality of pain control in the long term during the patient follow-up. The recognition of neuropathic pain demands a prompt, careful evaluation of any kind of painful symptom, possibly with the aid of dedicated questionnaires [79].

CONCLUSION

Clear evidence on the optimal postoperative analgesia for VATS is still lacking, and it would be presumptuous to provide universal recommendations that fit all centres and patients. More studies on the subject are warranted. From the evidence gathered, however, the imperative to resort to multimodal strategies (Table 1) remains valid to minimize invasiveness and adverse effects of each drug or technique.

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