Editorial

Analgesic management after thoracoscopic surgery: recent studies and our experience

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Provenance: This is an invited Editorial commissioned by the Section Editor Laura Chiara Guglielmetti (University Hospital Zurich, Zurich, Switzerland).

Comment on: Umari M, Carpanese V, Moro V, *et al.* Postoperative analgesia after pulmonary resection with a focus on video-assisted thoracoscopic surgery. Eur J Cardiothorac Surg 2017. [Epub ahead of print].

Submitted Mar 24, 2018. Accepted for publication Mar 31, 2018.
doi: 10.21037/jtd.2018.04.34
View this article at: http://dx.doi.org/10.21037/jtd.2018.04.34

Thoracoscopic surgery (TS) is a less invasive procedure than open thoracotomy because it involves less postoperative pain, a lower complication rate, a shorter time to ambulation, and shorter hospitalization. Clinically, patients who undergo TS do not always harbor mild-to-moderate postoperative pain. Additionally, the insufficient management of postoperative pain might lead to the development of chronic pain. We previously reported that individual pain scores after TS are classified as no and mild (0–3/10), moderate (4–6/10), and severe (7–10/10) using the numerous rating scale (NRS). In an analysis of 524 patients who underwent TS, the incidence of mild pain was 87.0% on the operative day and 75.6% during ambulation (1). The mean NRS score after TS in patients who received a single-shot intercostal nerve block (INB) using ropivacaine was 1.83±1.49 on the operative day, 2.73±1.75 during ambulation, and 1.87±1.33 during settling, after receiving several analgesic drugs after TS, whereas the mean NRS score was 3.05±1.51 during ambulation after open thoracotomy in patients who received paravertebral block (PVB) or epidural analgesia (EA); thus, pain scores were significantly higher after open thoracotomy than TS ($P<0.01$) (1).

However, there is still no consensus regarding optimal pain management after TS. In the present editorial, we focus on clinical acute post-thoracoscopic pain (APTP) and chronic post-thoracoscopic pain (CPTP) management after TS with reference to recent studies and our experience.

APTP

APTP after TS, including neuropathic pain, is likely a type of nociceptive pain that occurs from tissue trauma. Nociceptive pain occurs when thoracic tissues, such as intercostal muscles, pleura, ribs, and intercostal nerves, are impaired, and the continuous stimulus is perceived as painful. In our previous data, 13.0% and 24.4% of patients experienced moderate or severe pain on the operative day and during ambulation, respectively, and those patients with pain had a higher probability of requiring plural analgesics (1). Kaplowitz *et al.* determined that acute control is important for the following two reasons: to prevent splinting and stretching of the surgical incisions as a result of breathing and to help provide effective pre-emptive analgesia (2).

Regional analgesia (EA/PVB/INB/multimodal analgesic regimen)

EA

EA is the gold standard for thoracotomy. In 312 patients who underwent pneumonectomy at the 24 United Kingdom thoracic surgical centers in 2005, the most common type of analgesia used was epidural (61.1%), followed by paravertebral infusion (31%) (3). Despite being the most common analgesia after thoracic surgery, its frequent side effects, including urinary retention (42%), nausea (22%), itching (22%), and hypotension as a result of decreased

sympathetic tone (3%), are sometimes held in question (4). Recently, regarding thoracic anesthesia, many studies comparing EA with PVB that measured the analgesic efficacy or complications were conducted. A meta-analysis of randomized controlled trials (RCTs) was conducted to resolve the clinical question of whether PVB is as effective as EA for pain management in patients undergoing thoracic surgery, and they concluded that intercostal analgesia in the form of PVB is at least as effective as EA (5). It is unclear whether there is an analgesic benefit of EA for TS.

One RCT of a small sample of TS lobectomies (n=52) reported equivocal findings for the pain scores, analgesic requirements, pulmonary function, satisfaction score, and the incidence of side effects when EA using 0.2% ropivacaine with fentanyl was compared with intravenous (IV) patient-controlled analgesia using fentanyl and ketorolac (6). Another RCT of a small sample of TS lobectomies and wedge resections (n=46) reported that EA is effective for pain control until one postoperative day after TS, particularly for pain during movement. However, that study reported that EA causes nausea/vomiting in some patients when EA using 0.1% bupivacaine with fentanyl was compared with non-EA involving diclofenac, pentazocine, and loxoprofen (7). A recent RCT of a small number of predominant TS wedge resections (n=62) reported equivocal findings for pain relief when EA and INB using both ropivacaine was compared (8). Although these studies were small number referring to the use of EA after TS, it should be impossible to determine the definitive conclusion. One review commented that on the basis of available data, EA is likely not necessary for patients undergoing TS, and situations in which EA may be considered include a high likelihood of conversion to thoracotomy and an opioid-tolerant patient (2).

To summarize, based on our literature analysis, there is no clear evidence to support the superiority of EA for TS compared with other analgesic management methods to prevent a higher rate of side effects.

PVB

Various PVB catheter insertion techniques, such as ultrasound-guided, percutaneous, computed tomography-guided, and stimulation methods, have been described, but the rate of insertion failure ranges from 6% to 10% (5). Many meta-analyses and reviews comparing EA and PVB have emphasized that the use of PVB after thoracic surgery is at least as effective as that of EA for APTP management; moreover, there are fewer side effects with PVB (2,5). A large retrospective cohort study (n=1,592) reported that PVB with morphine patient-controlled analgesia seems as effective as EA for reducing the risk of postoperative complications, and the authors additionally found that the use of PVB is associated with a shorter hospital stay and that PVB may be a better form of analgesia for fast-track thoracic surgery (9). PVB directly affects only the unilateral paravertebral space structures, including the intercostal nerve and vessels, dorsal ramus, rami communications, and thoracic sympathetic nerve (5). Therefore, PVB has a reduced risk of significant side effects compared with EA. Therefore, if possible, PVB should be used as an alternative for thoracic surgery to avoid EA. However, in our previous data, NRS was found to be significantly higher in patients undergoing thoracotomy who received PVB than in patients undergoing TS with INB instead of PVB (1). It is doubtful whether there is an analgesic benefit of PVB for TS.

Review of gathering RCTs of a small number of patients undergoing TS (n=50–77) reported improved pain scores and reduced analgesic requirements when PVB using bupivacaine was compared with that using placebo (2). One RCT of a small number of TS lobectomies (n=41) reported equivocal findings for pain relief and additional analgesic consumption when both PVB and EA using 0.25% bupivacaine was compared; however, PVB had a better safety profile than EA (10). One RCT on TS wedge resection and pleural or lung biopsies in a small population (n=50) reported equivocal findings for pain relief when a single injection of PVB was compared with multiple injections, both of which methods included 0.5% bupivacaine (11). One RCT of a small number of TS lobectomies (n=61) reported improved dynamic pain relief and reduced morphine consumption when PVB and local wound infiltration using both 0.5% ropivacaine was compared (12).

To summarize, PVB is a viable option after TS, either alone or as part of a multimodal combination, for nociceptive pain and reduced opioid consumption; however, the failure rate of the catheter insertion is not rare. PVB may play a major role in nociceptive pain management after TS, according to the existing literature, although further large-scale investigations regarding the effectiveness of PVB are necessary.

INB

Analgesics can be injected through the pleura from inside the chest toward the multiple intercostal spaces at the end of TS under direct visualization. This method is used to avoid

injection of the definitive dose into the intercostal vessel. As mentioned previously, we found strong support showing that the analgesic regimen combining INB and non-opioid medications provides an excellent level of pain control after TS and plays an essential role in early ambulation. In addition, the clinical evaluation of INB is less clear than those of EA or PVB.

One prospective observational cohort of a small number of TS lobectomies (n=48) reported that acute pain may be adequately controlled using a multimodal non-opioid regime (0.25% bupivacaine) that includes PVB and an intercostal catheter (13). A large retrospective study on single-port TS-predominant wedge resections (n=235) reported improved pain relief and a shorter hospital stay when a multimodal regime with INB using 0.2% levobupivacaine was compared with that without INB (14). One RCT of a small number of TS mediastinal lymph node biopsies (n=60) reported improved pain control and reduced morphine consumption when a multimodal regime with INB using 0.25% bupivacaine was compared with that without INB (15). Another retrospective and prospective study on TS biopsies reported improved pain relief and dramatically reduced morphine consumption when a multimodal regime with INB using 0.25% bupivacaine was compared with that without INB (16). One RCT of a small number of TS-predominant wedge resections (n=48) reported prolonged pain relief and superior patient satisfaction when PVB one-shot INB using both either 0.25% or 0.5% bupivacaine was compared (17).

To summarize, based on the existing literature, INB is effective if used as directed, and it improves pain relief and reduces opioid consumption. In addition, our recommendation for APTP management is the use of single-shot INB as part of multimodal analgesia because of its safe, feasible, and plane nature. It is currently inexplicable to define INB as the first or second choice in APTP after TS lobectomy. The existing data may be biased because the patient populations were small and TS wedge resection was predominant.

Multimodal analgesic regimen

Non-opioids

The usefulness and effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) have been histologically commended for postoperative pain control both in thoracic surgery and in surgery in other organs. After the surgical incision, the first pain sensation is mostly nociceptive; commonly, the use of NSAIDs is theoretical. One RCT of a small number of TS wedge resections (n=40) reported improved pain relief and reduced morphine consumption when PVB with ropivacaine was compared with IV NSAIDs using paracetamol plus metamizol (18). The authors concluded that the analgesic regimen combining PVB and NSAID provides an excellent level of pain control (19). A relatively large retrospective study on predominant TS lobectomies (n=185) reported that the most significant contribution of PVB using 0.5% bupivacaine or 0.2% ropivacaine plus oral NSAIDs to enhance recovery was due to effective analgesia and fewer side effects (19).

When warned, patients with renal dysfunction or a history of gastrointestinal bleeding refrain from consuming NSAIDs to prevent symptomatic deterioration. The use of acetaminophen, particularly IV acetaminophen (paracetamol), for postoperative pain management has been advocated as an alternative to NSAIDs. Although the exact site and mechanism of action of acetaminophen are not clearly defined, the central nervous system is the active compartment, and it likely involves central COX inhibition and cannabinoidergic effects, along with indirect analgesic serotoninergic effects (20). Various meta-analyses and literature reviews across a variety of surgical procedures have reported that the perioperative administration of IV acetaminophen results in the superiority of postoperative pain control and a greater reduction in total morphine consumption (20). In our retrospective study, the reduction in pain in 524 patients with an NRS score ≥1 who underwent various TS procedures was significant with the addition of pentazocine hydrochloride ($P<0.01$) and flurbiprofen ($P<0.01$) (1).

Weak and strong opioids

Based on our previous analyses of 524 patients, the requirement for strong opioids post operation was not recognized at all, but significant differences were observed in the efficacy of desirable pain control regarding a dramatic NRS score reduction of ≥3; tramadol had a borderline tendency of efficacy as an additional prescription ($P=0.05$) (1). Kim *et al.*'s results supported our data (21). Postoperative weak opioid administration is clinically considerable for patients undergoing TS, particularly if the patient complains about severe pain. Continuous pain as a consequence of inadequate nociceptive pain control can lead to potential persistent intercostal neuralgia or CPTP, which might be significantly associated with patient discomfort. Tramadol with a weak affinity for the μ-opioid receptor and the metabolite with a relatively higher affinity contribute to pain relief, whereas tramadol stimulates the presynaptic

release of serotonin and inhibits the uptake of serotonin and norepinephrine. Thus, tramadol may enhance both nociceptive and intercostal neuralgia via these different mechanisms.

Optional adjuvant

Pregabalin contributes to multimodal pain control tactics as an adjuvant medication. Similar to other gabapentinoids, pregabalin reduces the hyperexcitability of the dorsal horn neurons induced by damage rather than reducing the afferent input from the site of the tissue injury, and it inhibits the release of excitatory neurotransmitters, including glutamate, noradrenalin, and substance P (21). One RCT of a small number of TS-predominant wedge resections (n=60) reported an improved postoperative pain score and reduced rescue analgesics when the postoperative use of pregabalin (150 mg) was compared with placebo (21).

To summarize, as a means to reduce postoperative opioid consumption, a multimodal analgesia combination of plural medications and regional blockage for nociceptive pain management is recommended. We believe this pain management method to be relevant given the analyses showing the uncontrolled postoperative pain that is observed after TS.

CPTP

CPTP, including allodynia, is common and unusually severe, but it can occur after TS. Continued pain simulation can lead to hyperexcitability of the nerves in the central nervous system and the activation of N-methyl-D-aspartic acid receptors, resulting in central sensitization, which may lead to a higher incidence of CPTP (2). Patients suffering from CPTP closely correspond to neuropathic pain due to damage of the intercostal nerves. Unlike postoperative nociceptive pain, lesions to the peripheral nervous system can produce persistent maladaptive plasticity (22). Intensity of acute postoperative pain correlates with the risk of CPTP. Intraoperative impairment of the intercostal nerves, including stretching, transaction of their cutaneous branches, and trauma produced by muscle resection and rib retractors, has long been considered the main factor of postoperative neuropathic pain in thoracic surgery (23). Previous reports have shown improved nociceptive pain and CPTP when minimally invasive approaches, such as TS and anterior thoracotomy, are used, compared with conventional thoracotomy (23). However, a clinical experiment revealed that either the amount of intraoperative intercostal nerve damage is not indicative of long-term nerve damage or that there is a more significant cause of chronic pain other than intercostal nerve injury (24). There is a potential entity of more complicated mechanisms for CPTP beyond the simple assumption of intercostal nerve damage. Most previous studies have focused on CPTP after thoracotomy, and few address the preventive effects of analgesic techniques on CPTP after TS. Meta-analyses of RCTs have indicated that EA may reduce the risk of developing chronic pain after thoracotomy (25).

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Kuroda H, Sakao Y. Analgesic management after thoracoscopic surgery: recent studies and our experience. J Thorac Dis 2018;10(Suppl 9):S1050-S1054. doi: 10.21037/jtd.2018.04.34

