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Achieving pain control with opioid-sparing multimodal analgesic strategy – doing more with less by enhanced recovery after thoracic surgery protocol: A Review

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Abstract

In the last decade, the implementation of enhanced recovery protocol for patients undergoing thoracic surgical procedures, either by thoracotomy or thoracoscopy, has gained significant recognition. Such protocols have been developed following the enhanced recovery after surgery (ERAS) guiding principles, yet have been tailored with attention to the unique nuances of thoracic surgical patients. Over the last 5 years, a body of literature has been published attesting to the success of the enhanced recovery after thoracic surgery (ERATS) protocol, with reported improvements of measurable outcome metrics. This mini-review focuses on postoperative pain control using the innovative strategy of opioid-sparing multimodal analgesics of the ERATS care pathway.

Pain and thoracic surgery

Acute pain

Acute postoperative pain is ubiquitous after surgical interventions, the magnitude and duration of which is dependent on the type of operation and patient characteristics. Thoracic surgical procedures, particularly those performed by thoracotomy, are associated with severe acute postoperative pain as well as unrelenting chronic post-thoracotomy discomfort in a high percentage of patients[1-3]. While minimally invasive thoracoscopic surgery (MITS) employs small incisions with no rib spreading retractors, causing less overall pain and higher patient satisfaction compared to thoracotomy[4,5], it is not entirely immune from causing acute postoperative discomfort and long-term chronic pain[1,4,6,7]. Chronic postsurgical pain is defined by the following criteria: 1) pain that developed after a surgical procedure, 2) pain of at least two months duration, 3) other causes of pain are excluded and 4) pain not caused by pre-existing conditions[8]. In 2006, Maguire and colleagues published the results of their survey conducted on 600 patients who had undergone thoracoscopy or thoracotomy over a period of seven years to assess for the prevalence of chronic pain after surgical interventions, the neuropathic contribution to their symptoms, and the impact on the patient's quality of life[9]. The authors demonstrated: 1) one year prevalence of chronic pain was reported equally after either thoracotomy (45%) or thoracoscopy (41%), 2) 39% of patients were taking analgesics, 3) 45% of patients reported pain as their worst medical problem and 39% reported limiting their daily activities, 4) the prevalence of neuropathic symptoms is between 35% to 83% of the cases and 5) nerve dysfunction is associated with more severe, persistent pain. Many studies have demonstrated that at 6 months, the only independent predictor of chronic pain following thoracic surgery is the severity of acute postoperative pain during the initial three days after surgery[2,10]. Whether or not the optimal analgesic management of acute postoperative pain would significantly reduce or even eliminate chronic pain following thoracic surgery remains yet to be determined [1 and references therein].

Chronic pain

In addition to incisional pain, another form of pain affecting thoracic surgical patients is neuropathic pain, which is defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system"[11,12]. Neuropathic pain is characterized by moderate to severe discomfort such as burning, electric shock sensation, and significant numbness, with sensory loss of skin dermatomes distal to the surgical scars. The incidence of neuropathic pain in patients with chronic pain after surgery is approximately 25% to 50%[6,11,12]. One of the challenges in managing and diagnosing patients with neuropathic pain is the heterogeneity and lack of pathognomonic symptoms. Patients tend to erroneously describe the neuropathic symptoms as the common term "pain", often misinterpreted by health care professionals as somatic pain. Unless the patient is specifically prompted further on details regarding the quality and location, the neurogenic "pain" can be inappropriately managed by opioid analgesics[6].

Intercostal nerve injury appears to be the most important factor leading to chronic neuropathic pain. This is particularly prevalent following traditional thoracotomy, attributed to significant intercostal nerve traction and pressure by metal retractors and pericostal rib closure. Modification of thoracotomy techniques, such as mobilizing the intercostal muscle and its neurovascular bundle to avoid direct pressure from the retractor, have shown to reduce the postoperative pain acuity and narcotic use up to 3 months after thoracotomy[13,14]. Another modification to avoid chronic neuropathy is the intracostal rib closure which includes drilling holes in the rib through which the closure sutures are passed instead of encircling the neurovascular bundle as traditionally performed. This technique has been shown to be associated with reduced acute and chronic postoperative pain up to 3 months[15,16]. Thoracic surgery has evolved and the hallmark of minimally invasive thorascopic surgery is small incisions of less than 8 cm without rib retraction and two 5-mm port incisions[17]. Despite the smaller incision sizes, plastic wound protectors used for retraction, and the traction caused by the rigid instruments and trocars inserted through the intercostal muscles can still cause pressure injury to the intercostal nerves.

Traditional management of acute pain after thoracic surgery

The intensity and duration of acute postoperative pain following thoracic surgical procedures is a major source of anxiety for patients and may contribute to postoperative complications. Inadequately controlled postoperative pain leads to less mobilization, decreased ambulation, as well as ineffective chest physiotherapy and cough responses. Such physical limitations coupled with the acute decrease of lung function following lung resection, particularly in those with reduced pre-existing reduced pulmonary reserve due to smoking-induced emphysema, have significantly increased the risk of respiratory complications. Therefore, adequate pain control is an essential component of the postoperative care protocol for thoracic surgical patients.

A pain regimen that relies heavily on potent opiate medication can be hampered by side effects including but not limited to drowsiness, delayed return of bowel, bladder function, nausea/emesis. Theses side effects contribute to increased risk for atelectasis/hypoxemia, pneumonia, deep vein thrombosis, prolongation of hospitalization and reduced patient satisfaction. Post-operative acute pain management in the 1970's and 80's was limited, vastly ineffective, and burdened with side effects due to the use of intra-muscular opioids such as Demerol or morphine. Evolving pain control regimens have included intravenous morphine or hydromorphone patient-control analgesia (PCA), which had the advantage of offering timely self-administered analgesics with less side effects, particularly opioid-induced somnolence and respiratory depression[18,19,20]. Thoracic epidural (TEA) is another technique that has commonly been regarded as the gold standard in postoperative pain management, as it offers the advantage of combining a continuous basal rate of infusion (with or without additional PCA), local anesthetic (such as bupivacaine), and an opioid[18, 21, 22]. While being very effective when functioning correctly, TEA is associated with several potential complications including sympathetic blockade, hypotension, inadvertent intrathecal injection, epidural hematoma, and catheter malfunction[22-24]. Catheter misplacement leads to incomplete pain control and can pose a challenge in care as the management of TEA is frequently provided by the acute pain anesthesia service and not the surgical team. Successful epidural catheter placement is operator-dependent and influenced by patient body habitus [Manion]. Recently, an alternative form of regional analgesia, such as paravertebral block has been gaining attention with increasing evidence that as effective as epidural analgesia[25,26]. However, these approaches can be labor-intensive, and more importantly patient-unfriendly since the placement the infusion catheter is usually performed on awake patients receiving mild conscious intravenous sedation. Until the recent adoption of ERATS and its opioid-sparing multimodal analgesic regime, the above-mentioned pain control techniques in addition to intravenous and oral potent opioids have been the backbone of postoperative pain management for thoracic patients.

Importantly, the high incidence of persistent opioid use, which is a public health concern, is a challenging aspect of pain management after thoracic surgery. Opioid-naïve is defined as no opioid prescriptions filled between 12 months and 31 days before surgery whereas new persistent opioid use is defined as a previously opioid-naïve patient who fills an opioid prescription attributed to surgery in addition to at least one other opioid prescription between 91 to 180 days after surgery[8]. In a comprehensive population-based cohort study (39,140 opioid-naïve patients ≥ 66 years old) evaluating the rates and risk factors for prolonged opioid use after major surgery (cardiac, thoracic, intraabdominal and pelvic procedures), Clarke and associates demonstrated that patients undergoing thoracic surgical procedures had the highest rates of persistent opioid use (thoracotomy 8.5% and thoracoscopy 6.3%) compared to radical prostatectomy (2.8%), coronary artery bypass by sternotomy (3.3%), colorectal surgery (open 2.8% and minimally invasive 3.2%)[27]. Moreover,14% to 18% of opioid-naive patients undergoing lung cancer resection are persistent opioid users[28-31]. Some of the risk factors associated with persistent opioid use include male gender, young age (<64 years), thoracotomy (versus thoracoscopy), adjuvant chemotherapy or radiotherapy, and chronic postoperative pain, which could had been modified by effective early postoperative acute pain management.

The pandemic of over-prescription of opioids in postoperative patients is a well-documented issue[32,33]. Not only is there an increased risk for persistent opioid use in surgical patients, but also these are frequently over dispensed and not utilized, predisposing to diversion and abuse by others than the intended recipients[33]. In a systemic review of opioid utilization in patients undergoing thoracic, orthopedic, obstetrics and general surgical procedures, Bicket and colleagues reported that of all the opioid tablets obtained by patients, 42% to 71% went unused, mainly due to adequate pain control and/or concerns for side effects. Furthermore, the authors state that 73% to 77% of patients reported that their unused opioids were not stored properly in locked containers increasing the risk for misuse[32]. Guidelines for improved postoperative opioid prescribing practices have been developed for general surgery patients, leading to substantial reduction of the amount of opioid prescribed without affecting pain control[33,34]. Therefore an innovative opioid-sparing analgesic strategy approach to minimize acute post thoracic surgery pain, thereby reducing the risk of chronic pain and persistent opioid use, would have the potential of significantly curtailing opioid need in the post-operative period. This is exactly the overarching therapeutic goal of the enhanced recovery after thoracic surgery (ERATS) protocol.

Enhanced Recovery after Thoracic Surgery (ERATS)

The ERAS® society and the European Society of Thoracic Surgery published guidelines for enhanced recovery after lung surgery with recommendations for 45 items that cover pre-admission, admission, intraoperative care, and postoperative care[35]. The ERAS concept, developed in early 2000's by clinicians in Europe as a care protocol, addresses pre-, peri- and post-operative components of surgical patients with an overarching goal of achieving optimal postoperative outcomes and safe discharge while being cost-effective[36]. The principle of ERAS is the multidisciplinary, patient-centered approach to resolve issues that cause complications to accomplish quality post-operative recovery. This aim is achieved by systemically applying evidence-based practice, formatted into a care protocol with built-in frequent updates to optimize quality improvements. One important feature of ERAS is a built-in internal auditing process to ensure compliance and achievement of desired patient outcomes following implementation. The principles of ERAS were maintained in the development and implementation of post-operative care pathways for thoracic patients. Table 1 summarizes the ERATS protocol developed and implemented at our institution, which is similar to those utilized in other groups[37-41] The aim of ERATS is to standardize and streamline all aspects of care for thoracic patients to achieve optimal pain control, lower postoperative complications, on-time discharge (i.e. shortest possible hospital stay), decreased opioid utilization, and cost-effectiveness. While all components of ERATS synergistically contribute to the desired outcomes, satisfactory pain control is most pertinent to thoracic surgical patients. In our opinion, the use of a long-acting preparation of local anesthetic agent such as liposomal bupivacaine (Exparel®, Pacira Pharmaceuticals, Inc., Parsippany, NJ) for direct intercostal nerve blocks, as advocated by Mehran and colleagues[42,43] has changed our practice of post-thoracotomy, post-thoracoscopy pain control. The management of acute postoperative pain is streamlined by elimination of patient-controlled thoracic epidural analgesia and minimizing intravenous opioids. Ultimately, this allows the surgical team to provide a "real-time" assessment of patient pain levels and the ability to intervene and administer appropriate measures for improved pain control. Minimizing post-discharge narcotic dispense reduces opiate availability to the public and contributes to the fight against the opioid abuse epidemic in the USA and other parts of the world. The overall reduction of postoperative opioid use following ERATS

Table 1: Outline of the ERAT protocol at the University of Miami Health System

Preoperative phase – surgeon and anesthesia team
Preoperative evaluation and management of modifiable co-morbidities
Counseling and set realistic expectations of postoperative recovery, reading materials
Carbohydrate drinks
Perioperative phase: surgeons and anesthesia team
Oral analgesics
Antibiotic wound prophylaxis
Mechanical/pharmacological DVT prophylaxis
Anesthesia cares: euvolemia, postoperative nausea/vomiting prophylaxis, avoid hypothermia, minimize volatile inhalational anesthetics
Intraoperative surgical wound infiltration and posterior intercostal nerve block with liposomal bupivacaine
Postoperative phase: surgeons and APRN / nursing team
Multimodal non-opioid analgesics: acetaminophen, NSAIDS (ibuprofen or ketorolac), gabapentin, tramadol and PRN schedule II opioids (morphine, oxycodone, hydromorphone), minimize or avoid the use of thoracic epidural analgesia
Out of bed/ambulation POD0
Regular diet
Removal of bladder catheter POD1/2
Remove chest drain once air leak stops and serosanguinous drainage volume <5 ml/kg/day
Urinary retention prophylaxis for men >50 years old: tamulosin 0.4 mg po starting POD0
Atrial fibrillation prophylaxis: continue perioperative betablocker otherwise start metoprolol 12.5 mg twice a day POD0 for anatomic lung resection
Intravenous fluid balanced salt solution 1 ml/kg/hr until void after bladder catheter removal
DVT prophylaxis: heparin SQ 5000 units q8hrs and intermittent pneumatic compression
GI prophylaxis: proton pump inhibitor, laxatives
Discharge planning: surgeons and APRN
Verbal and printed discharge instructions
Personalized discharge opioid prescription (tramadol and oxycodone or hydromorphone)
Multimodal non-opioid analgesics: acetaminophen, NSAIDS (ibuprofen or ketorolac), gabapentin

PRN: pro re nata / as needed; POD: postoperative day; SQ: subcutaneous; APRN: advanced practice registered nurse; DVT: dep vein thrombosis; GI: gastro-intestinal; NSAID: non-steroidal anti-inflammatory drug

implementation, as reviewed below, has been observed by many independent investigators.

Surgeon-driven posterior intercostal nerve block with liposomal bupivacaine

Intraoperative infiltration of multiple intercostal spaces and surgical incisions with local anesthetics such as bupivacaine with 1:200,000 epinephrine (up to 8 hours of therapeutic effect) is frequently used as regional analgesia for thoracic procedures. This approach is limited by the short duration of analgesia following a single administration of the local anesthetic unless continuous infusion with a pump/catheter system is employed. The therapeutic effect of bupivacaine can be prolonged to 72 hours by formulation with liposome as an extended-release preparation (Exparel®). The pharmacokinetics of liposomal bupivacaine offers an ideal therapeutic option for thoracic regional analgesia. This bupivacaine formulation combines long duration of action compatible with catheter-based techniques with the convenience of a single-shot nerve block. Mehran and colleagues (MD Anderson Cancer Center, Houston, Tx) evaluated the safety of liposomal bupivacaine posterior intercostal nerve block as part of ERATS in a retrospective cohort study; the technique is well described in their manuscript[42]. The authors reviewed 1737 patients who had undergone lung resection between 2010 to 2015. They performed two propensity-match analyses of postoperative events first in matched groups (618 each) with and without liposomal bupivacaine and second in matched thoracotomy patients (247 each) with or without liposomal bupivacaine (those patients had thoracic epidural catheter for postoperative analgesia). There were no increased adverse events, re-admission to intensive care unit and re-operation. However, there was a statistically significant reduction of hospital length of stay in the liposomal bupivacaine group in both propensity-matched analyses. In a separate retrospective analysis, Rice and colleagues, also from MD Anderson Cancer Center, compared the efficacy of liposomal bupivacaine intercostal nerve block in 54 ERATS patients with a propensity-matched cohort of 54 patients having thoracic epidural analgesia[43]. Their study showed no difference in pain scores, opioid consumption, and perioperative morbidity. There was no acute toxicity related to liposomal bupivacaine. The hospital length of stay was shorter in the liposomal bupivacaine group (mean of 3.5 days) versus the thoracic epidural control group (mean 4.5 days, p=0.004). Similarly, Medina and colleagues (University of Illinois, Peoria, IL) performed a comparative retrospective analysis of 95 VATS patients receiving liposomal bupivacaine intercostal nerve block with a propensity-matched cohort of 95 patients receiving thoracic epidural analgesia[44]. These authors observed a reduction of pain, less opioid use and lower total and direct hospital costs in the liposomal bupivacaine group. The hospital length of stay was similar between the two groups. Overall, liposomal bupivacaine intercostal nerve block within the context of ERATS provides a safe alternative to thoracic epidural analgesia in thoracic patients.

Review of published results of ERATS

Recently, our group reported the impact of ERATS on patients undergoing lung resections either by robotic video-assisted thoracoscopic surgery (R-VATS; 126 pre-ERATS versus 184 ERATS) or by open thoracotomy (pre-30 ERATS versus 32 ERATS) in a retrospective study using comparable cohorts of pre-ERATS patients as historical controls (study period: 1/1/2017 to 1/31/2019)[45]. Thoracic epidural analgesia was not used in thoracotomy patients. All patients received intraoperative posterior intercostal nerve blocks and infiltration of surgical wounds with liposomal bupivacaine. In the robotic thoracoscopy cohort, a 50% reduction of patient report pain (on POD0 to POD3) was observed following ERATS implementation that was coupled with a 38% reduction of in-hospital opioid utilization (median pre-ERATS of 30 MME versus median ERATS of 18.4 MME, $p = 0.009$) and a 66.7% reduction of opioid prescribed at hospital discharge (median pre-ERATS of 480 MME versus median ERATS of 150 MME, $p < 0.001$). In thoracotomy patients, significantly improved pain control was achieved with the multimodal analgesic strategy even in the absence of TEA in ERATS patients. Similar in-hospital opioid utilization was noted between the two cohorts, but there was a significant reduction of 83% in post-discharge opioid utilization (median pre-ERATS of 887 MME versus median ERATS of 150 MME, $p < 0.001$). More importantly, even with the lower total amount of post-discharge opioid prescribed, only 18.7% of ERATS patients needed a second or third opioid prescription refilled, which was significantly lower compared to 40% of those in the pre-ERATS group ($p = 0.01$). There was no difference in postoperative morbidly and hospital LOS in robotic or thoracotomy groups before or after ERATS implementation.

Martin and associates from the University of Virginia Health System (Charlottesville, Virginia) reported their early experience of implementing ERATS for patients undergoing lung resection by video assisted thoracoscopic surgery (VATS) (162 pre-ERATS patients versus 81 ERATS-VATS patients) or by thoracotomy (62 pre-ERATS patients versus 81 ERATS-T patients) in a retrospective study using comparable cohort of patients as historical controls (study period: 1/1/2015 to 5/1/2017)[38]. Liposomal bupivacaine intercostal nerve block was used on every patient with an additional single subarachnoid injection of preservative-free morphine for thoracotomy and VATS anatomic lung resection. There was significant 74% reduction of in-hospital opioid use (median pre-ERATS of 88 MME versus ERATS of 22 MME, $p < 0.0001$) with no difference in patient-reported pain, short-term postoperative complications, and hospital LOS in VATS patients. In thoracotomy patients, ERATS was associated with a 58% reduction of in-hospital opioid use (median pre-ERATS of 130 MME versus ERATS of 54 MME, $p < 0.0001$) and shorter hospital LOS, but no difference in pain levels. Most importantly, there was significant reduction of total hospital costs in both VATS and thoracotomy patients following ERATS implementation.

Haro and colleagues from the University of California at San Francisco (San Francisco, CA) reported the clinical results of their ERATS program[40]. In a prospective before/after cohort study involving 295 patients (169 pre-ERATS versus 126 ERATS) over a 3-year period from 10/2015 to 3/2019. ERATS implementation was associated with an increase in the use of thoracoscopic technique, reduction of intensive care unit admission, earlier removal of chest tube and bladder catheter, lower hospital LOS, less postoperative complications, and decrease in total hospital costs. Moreover, the authors reported an over all reduction of daily opioid use from 88 MME to 69 MME with the largest reduction (pre-ERATS of 74 MME versus ERATS of 46 MME) observed in patients undergoing minimally invasive surgery. However, contrary to our and others observations, the authors noted no difference in opioids use in thoracotomy patients (pre-ERATS of 108 MME versus ERATS of 108 MME).

Rice and colleagues, from MD Anderson Cancer Center, Houston, Tx recently performed a match-pairs comparison of an enhanced recovery pathway versus conventional management on opioid exposure and pain control in patients undergoing lung surgery by either VATS or open thoracotomy[46]. They 1:1 matched 125 ERATS patients using a cohort of 907 historical controls to form 123 pairs for comparative analysis. No thoracic epidural was used in ERATS patients and all had intercostal nerve block with liposomal bupivacaine compared to 66% and 16% in controls, respectively. There was a significant reduction of pulmonary complications and hospital LOS but not in-hospital mortality, 30- and 90-day morbidity following ERATS implementation. ERATS was associated with a drastic reduction of in-hospital MME (thoracotomy: pre-ERATS of 153.8 MME versus ERATS of 23.3 MME, $p < 0.001$; minimally invasive surgery: pre-ERATS of 100.7 MME versus ERATS of 17.5 MME, $p < 0.001$) and with more patients taking tramadol (a schedule IV opioid with low potential for dependency) both in-hospital and at discharge. There was a mild but statistically significant reduction of patient-reported pain levels in whole group ($p < 0.004$) and in thoracotomy subgroup (p=0.026) but not in VATS subgroup ($p = 0.09$). The salutary clinical impact of ERATS are summarized in Table 2.

Table 2: Clinical impacts of ERATS in patients undergoing thoracotomy or thoracoscopy procedures

Publications	N (Pre-ERATS)	N (ERATs)	Subjective Pain Levels	MME In-Hospital Opioid Use	MME Post-Discharge Opioid Use	Hospital LOS	Complications
Razi et al.[45]							
Thoracoscopy	126	184	↓↓↓	↓↓	↓↓	↔	↔
Thoracotomy	30	32	↓↓↓	↔	↓↓↓↓	↔	↔
Martin et al.[38]							
Thoracoscopy	162	81	↔	↓↓↓	NR	↓[a]	↔
Thoracotomy	62	58	↔	↓↓↓	NR	↓[b]	↔
Haro et al.[40]							
Thoracotomy& Thoracoscopy	169	126	NR	↓↓	NR	↓[b]	↓[b]
Rice et al.[46]							
Thoracoscopy	50*	50	↔	↓↓↓↓	NR	↓[b]	↓[b]
Thoracotomy	73*	73	↓	↓↓↓↓	NR	↓[b]	↓[b]

Definitions: ↔ No change; ↓ 0-25%; ↓↓ 25-49%; ↓↓↓ 50-74%; ↓↓↓↓ >75%. NR not recorded, ↓[a] Decrease in LOS or Complications but statistical significance was not reached, ↓[b] Decrease in LOS or Complications, but statistical significance was reached (MME: milligram of morphine equivalent; LOS: length of stay, ERATS: Enhanced Recovery After Thoracic Surgery)

* Data analyzed by Propensity Score Matching.

Summary and perspectives

Advances in the perioperative care and the surgical management of lung cancer patients have definite positive impacts on reducing operative morbidity and mortality in the last two decades[47]. Our collective review of published ERATS results demonstrates that such care pathway further improves postoperative outcomes, particularly drastic reduction of pain and opioid utilization in both thoracotomy and thoracoscopy patients while diminishing morbidity and hospital LOS in thoracotomy patients. When reported, ERATS also reduces hospital costs. This perioperative care protocol concurrently addresses acute pain control and opioid utilization, both of which is potentially crucial in diminishing chronic pain and persistent opioid use following thoracic surgery. The true impact of ERATS on these important issues needs careful long-term study.

Abbreviations

ERATS - Enhanced Recovery After Thoracic Surgery

MME – Morphine Milligram Equivalent

R-VATS – Robotic Video Assisted Thoracic Surgery

VATS - Video Assisted Thoracic Surgery

LOS – Length of Stay

Conflict of Interest

The authors declare no conflict of interest pertaining to the preparation of this manuscript.

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