Prehabilitation and enhanced recovery after thoracic surgery: a narrative review

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Background and Objective: Over the past two decades enhanced recovery after surgery (ERAS) pathways, which were established initially in colorectal surgery, have evolved and been adapted for other surgical disciplines. Goals include minimizing complications, optimizing recovery and an efficient return to preoperative baseline functioning. The introduction of ERAS pathways has led to both clinical benefits as well as cost savings. As these pathways consist of bundles of interventions throughout the perioperative period, the relative contribution of each individual component of these programs remains to be elucidated. The following narrative review article explores the application of ERAS principles to the thoracic surgery population. The evidence for individual components of these pathways will be discussed. Additionally, the introduction of prehabilitation interventions to the care of these patients will be explored. A brief case example is provided to illustrate how such interventions can aid in perioperative decision making.

Methods: Medical computerized databases (PubMed and Cochrane Library) were searched for relevant reviews and guidelines published in English up to March 31, 2021, and hand searches of the references were performed. Articles were reviewed but no formal statistical analysis was undertaken.

Key Content and Findings: Preoperative, intraoperative and postoperative elements of ERAS pathways were examined. Some elements, such as smoking cessation, have fairly robust evidence of benefit, but questions still remain regarding optimal duration of intervention especially when weighed against surgical delay. Others, for example preoperative carbohydrate loading, may lack significant evidence of improved outcomes but have been adopted widely because of ow perceived risk of harm. Formal prehabilitation programs show promise, particularly in the lung resection population.

Conclusions: Implementation of ERAS pathways has benefited thoracic surgical patients, however there is varying strength with regards to the evidence for individual components. There is an ongoing need to better define the roles of individual elements of these pathways and to further advance knowledge regarding the optimal ways in which to apply some of them.

Keywords: Enhanced recovery after surgery (ERAS); enhance recovery; prehabilitation

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Introduction

Enhanced recovery after surgery (ERAS) is a multidisciplinary approach to transition patients through the surgical period with an emphasis on evidence-based interventions to minimize complications, optimize recovery and return to baseline function efficiently. ERAS pathway interventions range from those intended to streamline organizational elements to those that aim to reduce the endocrine and inflammatory elements of the surgical stress response and maintain anabolic homeostasis (1). ERAS protocols evolved initially in the setting of colorectal surgery two decades ago with well-established benefits. These benefits are now being expanded to other surgical disciplines, with cost savings and decreased complications demonstrated at our own institution (Montreal General Hospital) by implementing ERAS pathways in both lung resection and esophagectomy programs (2,3).

Guideline recommendations have been published by the ERAS society for specific surgical procedures (lung resection, esophagectomy) (4,5). As these pathways consist of bundles of interventions throughout the perioperative period, the relative contribution of each individual component of these programs remains to be elucidated. The aim of this article is to summarize the current state of the literature on various individual elements of ERAS pathways in thoracic surgery in both lung resection and esophagectomy populations, including evidence for the role of prehabilitation interventions. While the esophagectomy and lung resection populations do differ substantially in pathology, surgery and perioperative complications, they are both common thoracic surgical procedures to which ERAS principles have been applied and both will be discussed in this review. Prehabilitation is a preoperative intervention that provides an opportunity to address and intervene on modifiable risk factors for adverse perioperative outcomes. A short case to illustrate how prehabilitation programs may aid in decision making will be included in Appendix 1. We present this article in accordance with the Narrative Review reporting checklist (available at https://ccts.amegroups.com/article/view/10.21037/ccts-21-24/rc).

Methods

Medical computerized databases were searched for relevant systematic reviews, meta-analyses, guidelines and individual trials through March 2021 using the terms "enhanced recovery after surgery", "ERAS", "prehabilitation", "thoracic surgery", "lung resection" and "esophagectomy". Articles that explored the risks, benefits and outcomes of ERAS programs or their individual components were included. Individual hand searches of the references were undertaken to provide additional sources on individual elements of the ERAS pathways. Articles referring to the non-thoracic surgical population were excluded, except where specifically mentioned due to a lack of thoracic surgery-specific literature. No formal statistical analysis was undertaken. The methods are outlined in *Table 1*.

Discussion

ERAS pathways may intuitively be divided into three main categories: preoperative, intraoperative and postoperative with *Table 2* showing some key elements of each category. While robust evidence exists for the benefit of bundles of these interventions, the quality of evidence supporting each individual intervention alone varies in strength and will be explored.

Perioperative nutrition

Nutrition plays a major role in improving wound healing, immunity, respiratory muscle strength and mitigating the consequences of protein catabolism induced by the perioperative stress response (6,7). Malnutrition is of particular interest because it is prevalent, particularly in the esophagectomy population, and potentially modifiable. Malnutrition is predictive of reoperation, respiratory complications and overall poorer surgical prognosis post esophagectomy (8). Nutritional supplementation starting only 5 days preoperatively in lung resection surgery was demonstrated retrospectively to reduce postoperative complications including bowel function recovery and respiratory failure, length of hospital stay (LOS) and hospital costs (9). Interest is emerging in immunonutrition (supplementation with formulations that include arginine and omega-3 fatty acids such as the impact formula from Nestle Health Science), with results from a small randomized controlled trial (RCT) showing decreased postoperative infectious complications including pneumonia in esophagectomy patients (10).

When part of a multimodal prehabilitation approach combining nutrition and exercise for a median of duration of 36 days prior to surgery, an RCT in esophagectomy patients showed an improvement in functional capacity that persisted postoperatively (11). Whether delaying cancer

Table 1 Search strategy summary

Items	Specification
Date of search	March 31st, 2021
Databases and other sources searched	PubMed and the Cochrane Library were searched, and hand searches of the references of individual articles were perform
Search terms used	Enhanced recovery after surgery, ERAS, prehabilitation, thoracic surgery, lung resection and esophagectomy
Timeframe	Up to and including March 31st, 2021
Inclusion and exclusion criteria	Systematic reviews, meta-analyses, guidelines and individual trials published in English were considered for inclusion
Selection process	Both authors collaborated on the search and independently reviewed articles for eligibility

ERAS, enhanced recovery after surgery.

Table 2 Outline of some elements of enhanced recovery in thoracic surgery

Preoperative
Nutrition
Smoking cessation
Anemia correction
Preoperative fasting and carbohydrate loading
Prehabilitation
Intraoperative
Prevention of venous thromboembolism
Prevention of surgical site infection
Temperature management
One lung ventilation
Anesthetic approach
Fluid management
Postoperative
Postoperative nausea and vomiting management and prevention
Atrial fibrillation prevention
Analgesia and regional anesthesia
Surgical technique
Chest drain management
Postoperative mobilization and physiotherapy

surgery to optimize nutritional status is an effective strategy to improve outcomes in more severely malnourished patients remains an interesting question. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend a 7- to 10-day period of enteral nutritional supplementation in severely malnourished patients [weight loss of 10–15%, body mass index (BMI) <18.5 kg/m^2, serum albumin <30 g/L in the absence of hepatic or renal dysfunction] (6).

Smoking cessation

The preoperative period surrounding thoracic surgery provides an effective opportunity to achieve smoking cessation (12) both for immediate reduction in perioperative risk as well as long term benefits. While smoking is a well-established risk factor for adverse surgical outcomes, the optimal duration of preoperative cessation and the expected gains with short durations of cessation have been debated (13,14). A decrease in postoperative pulmonary complications (PPCs) and intensive care unit (ICU) admission has been demonstrated among never *vs.* active smokers undergoing lung resection, however only a trend to reduced PPC and ICU admission was observed for ex-smokers with no difference between those who stopped more than or less than 6 weeks prior to surgery (15). Two large database studies have shown constant but gradual reduction in risk of PPCs (and in one study perioperative mortality) with increased duration of smoking cessation, with benefits seemingly continuing to increase with more than 1 year of cessation (14,16). While PPCs trended towards a decrease even with less than 1 month of cessation in both studies, this finding has not been reproduced consistently (17) and delaying surgery for the "full" benefit which may extend beyond 1 year is clearly not reasonable. Both for short and long-term benefits, it appears reasonable to counsel and actively support smoking cessation as soon as possible in the perioperative period.

The rise in popularity of vaping or electronic cigarettes raises interesting questions for the perioperative physician wishing to reduce harm from smoking. Current evidence does not clearly support their use as effective aids for smoking cessation (18,19), and moreover emerging concerns about vaping-associated lung injury may make them a potentially unsafe alternative to cigarettes (20).

Anemia correction

Preoperative anemia is a well-known risk factor for increased morbidity and mortality in lung resection surgery (21,22). In lung transplantation, anemia (as defined by hemoglobin (Hg) <12 g/dL in women and 13 g/dL in men) is associated with increased LOS and higher risk of bleeding requiring redo surgery (23). Preoperative anemia in esophagectomy was associated with acute respiratory failure in one retrospective study, and while not independently associated with adverse short-term outcomes, was associated with higher red blood cell (RBC) transfusions which increased the risk of overall complication and surgical site infections (SSIs) (17,24).

Some smaller RCTs, none specific to thoracic surgery, have evaluated the benefits of preoperative iron therapy. A recent meta-analysis showed reduced transfusions with preoperative intravenous (IV) iron therapy in anemic patients (25). The largest RCT to date, not included in the aforementioned meta-analysis, did not replicate these findings but was specific to abdominal procedures and was criticized for not specifically targeting iron deficient anemia and not outlining a transfusion strategy (26). Consensus guidelines recommend using iron studies to help identify iron deficiency, targeting normalized Hg values preoperatively and using IV iron when surgery is planned within 6 weeks (27). While ideally 4 weeks should elapse between the first dose and the surgery, statistically significant improvements in Hg maybe seen at 2 weeks post IV iron (25,26).

Preoperative fasting and carbohydrate (CHO) loading

The traditional "nil per os (NPO) from midnight" approach to preoperative fasting is no longer recommended. Data from RCTs supports both the safety and benefits of allowing clear fluids up to 2 hours before surgery (28,29). At our institution all patients except those at elevated risk of delayed gastric or esophageal emptying (e.g., type 1 diabetics, esophageal cancer, achalasia) are permitted clear fluids 2 hours before surgery.

CHO loading attenuates the insulin resistance, catabolism and hyperglycemia associated with the surgical stress response (30,31). Despite improved glycemic control and measures of patient comfort, there is conflicting or insufficient data regarding outcomes such as length of stay, infectious and overall complications (21,31-33). While data specific to thoracic surgery is lacking, a small study in the thoracic surgery population suggested improved postoperative pain and perhaps a trend to decreased nausea after CHO loading (34).

Overall preoperative CHO loading has been widely adopted by ERAS programs. The evidence for benefit in terms of preventing morbidity may be lacking but the safety profile and effect on quality of recovery appear favourable. More high-quality studies may be needed to further define the benefits.

At the Montreal General Hospital, all patients in whom clear fluids are not contraindicated within 2 hours of surgery are loaded with Precovery (Enhanced Medical Nutrition Inc.), a low-osmolality solution with 50 g of complex CHOs.

Prehabilitation programs

Decreased preoperative exercise capacity as measured by cardiopulmonary exercise testing (CPET) is a risk factor for postoperative cardiac and pulmonary morbidity as well as decreased long-term survival in thoracic surgery patients (35,36). The feasibility, safety and efficacy at improving functional capacity of preoperative prehabilitation exercise programs have been well demonstrated in several trials (37,38). Significant improvements in 6-minute walk test (6MWT) and anaerobic threshold on CPET have been demonstrated after 30-day interventions (37). Such an interval is feasible and does not add undue delay to operative waiting times if patients are referred for assessment by a prehabilitation team as soon as surgery is planned.

At our institution high-risk patients are identified using the 6MWT with a cut-off of 400 m and the Duke

Activity Status Index (DASI) score with a value of <34. Nutritional and psychological screening tools are also used as our prehabilitation program takes a multimodal approach. The goal of this intervention is to optimize preoperative physiological status in order to better withstand the insult of surgery and hasten the return to baseline functional capacity. An in-depth assessment allows for a very tailored program meeting the needs of the individual. A typical regimen would consist of a 4- to 6-week intervention combining and an either supervised or at-home aerobic and resistance exercise program, dietary intervention guided by a nutritionist, stress-reduction training and help with smoking-cessation.

A Cochrane review and a meta-analysis explore the postoperative outcomes of prehabilitation in lung resection surgery and report shorter length of stay, shorter chest tube duration and decreased complications (39,40). Most of the included studies had interventions that were of 4 weeks duration or less. To date there is less clear evidence for improved postoperative outcomes in the esophagectomy population, with a systematic review reporting mixed results but decreased PPCs in studies that included preoperative inspiratory muscle training (41).

Prevention of venous thromboembolism (VTE)

VTE post thoracic surgery is not uncommon (42,43), occurring at an estimated rate of 0.2–29% and predominantly in the first postoperative month in a recent review [although included studies were very heterogenous with regards to approach to prophylaxis and diagnosis of deep venous thrombosis (DVT) (44)]. In the absence of prophylaxis, a pulmonary embolism rate of 7% has been reported (45). Identified risk factors include age, operative time, decreased lung function and smoking history and BMI (42,43). Malignancy is also a well-known risk factor for VTE however and interestingly a recent large series of patients noted a prevalence of preoperative DVT in the lung cancer population of 9.6% (46). A systematic review in esophagectomy patients identified age, higher American Society of Anesthesiologists (ASA) class, history of cardiopulmonary disease and neoadjuvant chemo-radiotherapy as risk factors for postoperative VTE (47).

Several major guidelines exist addressing postoperative thromboprophylaxis strategies though not all address thoracic surgery specifically. The 2019 international clinical practice guidelines from the international initiative on thrombosis and cancer advisory panel recommend once daily low-molecular-weight heparin (LMWH) for cancer patients with (creatinine clearance >30 mL/min) or low-dose unfractionated heparin (UFH) three times a day commencing 2–12 hours preoperatively and continuing for 7–10 days, with mechanical monotherapy reserved for those with contraindications to anticoagulation (48). Of note, the most recent American Society of Regional Anesthesia and Pain Medicine guidelines permit indwelling neuraxial catheters with UFH 5,000 units SQ TID dosing (49). Extended prophylaxis of 4 weeks is recommended after major laparotomy or laparoscopy for higher risk patients with low bleeding risk (48). The American College of Chest Physicians (ACCP) guidelines propose an outline to determine individual patient risk, and recommend using either pharmacologic prophylaxis or intermittent pneumatic compression (IPC) for most thoracic surgery patients, and a combined pharmacologic/mechanical approach for high-risk patients and procedures (including extended resections, pneumonectomy and esophagectomy) who are not at major risk of bleeding (in which case IPC is favoured) (50). Extended prophylaxis is addressed only for abdominopelvic surgery, with a recommendation favouring 4 weeks of postoperative LMWH in high VTE risk cancer patients who are not at high major bleeding risk (50). Consensus regarding this practice has not been reached in the thoracic surgery world and practices vary widely.

Prevention of surgical site infection

SSI in thoracic surgery can be reduced by antibiotic prophylaxis and skin preparation. Good evidence supports the use of first generation cephalosporins such as cefazolin in a wide range of thoracic surgical procedures, whether or not a hollow viscus is entered (51). Guidelines recommend a dose of 2 g IV (3 g if >120 kg) be administered within 60 min of surgical incision and redosed every 4 hours with controversy regarding the benefit of continued dosing beyond the surgical period (52,53). Substitution with vancomycin or clindamycin is recommended for patients with beta-lactam allergy and vancomycin is recommended for patients known to be colonized with methicillin-resistant *Staphylococcus aureus* (MRSA) (52). As rates of cross-reactivity appear fairly low, in the absence of an IgE mediated reaction or exfoliative dermatitis with penicillins, cephalosporins can be administered safely (52,54). In our preoperative clinic we routinely arrange allergy testing for presumed penicillin allergic patients.

The evidence for prevention of postoperative pneumonia in thoracic surgery with current perioperative cephalosporin antibiotic regimens is less clear. Some advocate for alternative regimens based on susceptibility of organisms colonizing airways or longer duration of prophylaxis (55,56).

Preoperative skin bathing with antiseptic solution prior to surgery reduces skin colonization (57), but the superiority of antiseptics like chlorhexidine over soap or even placebo for actually preventing SSI is unproven and they may produce undesirable reactions and cost more (58,59). Guidelines recommend a presurgical wash with either soap or antiseptic (53). Hair removal by clipping, if necessary, appears to have a lower risk of SSI when compared with shaving, and in a larger RCT was noninferior to no hair removal (60,61). Presurgical skin preparation with chlorhexidine in alcohol is preferred to aqueous povidone-iodine solutions in patients without hypersensitivity (62).

Management of core temperature

Unintentional hypothermia, defined by body temperature below 36 ℃ is common in thoracic surgery with retrospective studies reporting an incidence of approximately 70% (63,64). Low body surface area, patient age, long anesthesia induction time and increased administration of fluids, ambient operating room (OR) temperature and the presence of a neuraxial catheter have been identified as risk factors in this population (63,64). Intraoperative hypothermia has been linked to decreased comfort, increased SSI, blood loss and LOS (65-67) and in the thoracic population the additional work of breathing associated with the metabolic demands of shivering on emergence is undesirable in many patients.

Guidelines recommend measuring intraoperative temperature in any surgery lasting 30 min or more (68) and effort should be made to maintain normothermia. Active warming techniques are superior to passive ones (blankets, socks) (69) but no clear evidence exists for a benefit of one type of active body surface warming over another (forced air *vs.* heated water blanket) (67). Prewarming with forced air for 15 min post epidural catheter placement is an effective approach, reducing incidence of hypothermia from 72% to 6% in one RCT in major abdominal surgery (70).

Lung isolation

Lung isolation for thoracic surgery is typically achieved via double lumen tube or bronchial blocker. While both devices achieve equivalent lung collapse for left sided surgery, the position of the right upper lobe may make a bronchial blocker less ideal for right sided surgery and they are more likely to require repositioning during the case (71). Neither device is clearly superior and use can be dictated by the setting and individual preference. While they may be associated with more sore throats (72) and may be more challenging to place in difficult airways, double lumen tubes have the advantage of enabling bronchoscopic inspection and suctioning of the operative lung without the need to deflate the blocker balloon.

Mechanical ventilation

Protective lung ventilation during one-lung ventilation (OLV), usually consisting of tidal volume (Vt) 4–6 mL/kg of predicted or ideal body weight (PBW) and positive end expiratory pressure (PEEP), has been widely adopted in thoracic surgery and while a meta-analysis demonstrated decreased PPCs (73), some recent studies have shed light on what elements may or may not actually be protective. A retrospective study included in the meta-analysis found that the likelihood of PPC decreased as Vt increased from 5 to 8 mL/kg PBW and while it may be hypothesized that the nonrandomized nature of this study led to lower Vt being used in more vulnerable patients, the effect was independent of compliance (74). One possible explanation lies in the fact that mean PEEP values were low in this cohort (4.2 cmH_2O) and without sufficient PEEP to prevent cyclic derecruitment the low Vt ventilation strategy was not truly protective. Increasing PEEP from 0 to 5 to 10 cmH_2O decreased shunt fraction and improved oxygenation but only at 10 cmH_2O suggesting that the PEEP levels used in other studies are not optimal in this patient population (75). Individualized titration with a decrement trial can be used to optimize PEEP levels and improve lung mechanics and oxygenation (76). Targeting the PEEP that results in the lowest driving pressure for a Vt of 6 mL/kg IBW was associated with decreased PPCs in an RCT (77). Alveolar recruitment maneuvers after initiation of OLV appear to improve oxygenation and reduce dead space ventilation and may also be considered to have a role in lung protective ventilation in thoracic surgery (78,79).

Elevated FiO_2 has been demonstrated to independently predict PPCs, and beyond the initial period where FiO_2 of 100% may be used to assist deflation of the operative lung, unnecessarily high FiO_2 should be avoided (80). Limited evidence suggests that re-expansion of the nonventilated lung with room air may attenuate tissue injury that may result from reactive oxygen species during the reperfusion of the lung (81-83).

Anesthetic technique

OLV is associated with the release of inflammatory mediators in both the ventilated and the non-ventilated lung, and there is evidence to suggest that this can be attenuated with volatile anesthetics as compared to total intravenous anesthesia (TIVA) with propofol (84,85). The clinical impact of this has been the subject of recent investigation. A multicenter RCT comparing TIVA to desflurane in lung surgery found no difference in major complications during hospitalization and 6 months after (86). Another RCT comparing sevoflurane to propofol in patients undergoing lung resection found lower PPC and mortality at 12 months in the sevoflurane group (87).

The authors prefer sevoflurane both for its bronchodilating effects and the larger body of evidence supporting the potential immunomodulatory benefits with regards to lung injury, unless there are strong risk factors for postoperative nausea and vomiting (PONV) in which case TIVA may be indicated. The optimal anesthetic regimen likely doesn't come down to choosing one particular technique, but instead depends on focusing on optimally managing pain while minimizing postoperative sedation and respiratory depression as well as minimizing unwanted side effects such as PONV. Sedating premedications are rarely needed, do not appear to improve patient experience (88), and should be used with caution in this often older population with compromised pulmonary function.

Perioperative fluid management

Fluid management in thoracic surgery deserves particular attention as this population is particularly vulnerable to pulmonary complications that can be exacerbated by overhydration. Postoperative acute lung injury (ALI) which is more prevalent in pneumonectomy and esophagectomy, has a high mortality rate and incidence correlates with higher levels of fluid administration (89). Fluid restriction on the other hand may put the patient at risk of organ hypoperfusion. Acute kidney injury (AKI) is reported to occur in approximately 6% of postoperative thoracic patients and is associated with increased reintubation, hospital LOS, ICU admission and mortality (90,91). Lower total fluid administration in observational studies of thoracic surgical patients has not been identified as a risk factor for AKI, with hydroxyethyl starches identified as risk factors in some studies (90-92). On the other hand, the results of a large international RCT showing increased SSI and need for renal replacement therapy, while limited to major abdominal surgery, certainly raise the alarm for overly restrictive approaches (93). A more moderate (neither "restrictive" nor "liberal") approach was shown to be beneficial in minimizing PPCs in the minimally invasive lung resection population (94). An approach aiming to target euvolemia with balanced crystalloid solutions appears a reasonable target.

Goal-directed therapy (GDT) is a strategy aimed at individualizing fluid administration aiming to optimize oxygen delivery guided by various hemodynamic parameters that indicate fluid responsiveness such as pulse pressure variation (PPV), systolic pressure variation (SPV) and changes in stroke volume (SV) or cardiac output (CO) with fluid challenges.

Many reviews and meta-analyses have pointed to a favourable effect of GDT on several postoperative outcomes, particularly in major intra-abdominal surgery (95,96). When GDT is used as part of an established ERAS pathway however, the benefits are less certain (96,97). Overall data specific to the thoracic surgery population is limited, and thoracic surgery poses some particular challenges as the open chest may interfere with dynamic blood pressure or SV responses to positive pressure ventilation and esophageal surgery precludes the use of transesophageal echocardiography or esophageal doppler monitoring (98,99). A small recent RCT evaluating GDT in esophageal resection using the FloTrac device showed no benefit in reducing postoperative complications, while an esophageal doppler guided study in lung resection patients showed reduction in PPCs and length of stay (100,101). Both studies designed their intervention arms in line with the recommendations of the anaesthesia working group of the ERAS society, whereby the intervention arm is fluid loaded until no more significant rise in SV can be detected even in the absence of clinical indicators of hypoperfusion or hypotension (102). Administering fluids when the patient is responsive but not necessarily requiring optimisation of perfusion could in theory promote iatrogenic injury, particularly in the thoracic population who may be additionally vulnerable to over hydration. Further studies are required to identify which patient populations within an ERAS framework, if any, would benefit most from these strategies and what the best parameters and algorithms are to avoid both overhydration and organ hypoperfusion.

In terms of fluid composition, in line with other ERAS guidelines, balanced crystalloid solutions are preferred to normal saline. While the debate between colloids and crystalloids is beyond the scope of this chapter, it should be noted in addition to the well-known impact on AKI in critically ill patients, associations have been demonstrated between AKI and hydroxyethyl starch administration in thoracic anesthesia (89,91).

PONV control

PONV is a common and distressing issue for patients. Well validated scores exist to stratify risk and should be applied to each case (103). While many thoracic surgery patients are smokers, which is protective, the typical requirement for postoperative opioids for these surgeries gives all thoracic surgery patients at least one risk factor. The fourth consensus PONV guideline take a more liberal approach to PONV prophylaxis, recommending 2 prophylactic agents even for patients with only 1 risk factor (103).

Beyond pharmacologic prophylaxis with the classic agents such as dexamethasone, 5-HT_3 receptor antagonists and dopamine antagonists, for which excellent evidence of efficacy exists, other interventions may be considered (103). These include minimizing preoperative fasting and dehydration, dexmedetomidine, sugammadex for reversal, use of propofol-based TIVA and optimal multimodal analgesia, including regional techniques such as epidurals and erector spinae blocks (103,104). When choosing between common agents it may be prudent to consider whether there will be another source of steroids, for example dexamethasone in intercostal blocks.

Atrial fibrillation prevention

Postoperative atrial fibrillation (POAF) complicates approximately 12–16% of thoracic surgeries, with a higher prevalence after bilobectomy or pneumonectomy, esophagectomy as well as surgery for higher stage disease (105-107). Other risk factors include male gender, age, race other than black, as well as higher brain natriuretic peptide (BNP) levels and $CHADS_2$ score (106-108). While many adverse perioperative outcomes have been associated with POAF, it is not clear to what degree the arrhythmia is a symptom or a cause of an adverse postoperative trajectory. While the majority of cases of perioperative atrial fibrillation are not thought to be sustained beyond several weeks (109), acute atrial fibrillation can certainly result in hemodynamic instability with organ hypoperfusion and heart failure, and a very large retrospective cohort study showed a significant increase in risk of stroke at 1 year in patients diagnosed with POAF (110).

The American Society for Thoracic Surgery (AATS) guidelines recommend at least 48 hours of ECG telemetry for higher risk patients. The only class I recommendation for prevention is the avoidance of beta blocker withdrawal for patients previously taking these agents (109). Replacement of low serum magnesium, a common finding in this population, is also recommended, and serum magnesium is part of our standard preoperative investigation panel for thoracic surgical patients (109). In higher risk patients, diltiazem or amiodarone may be considered (109). While concern exists for acute pulmonary toxicity with amiodarone use particularly in the pneumonectomy population, reports of such toxicity at doses currently recommended for prophylaxis are exceedingly rare (109).

Perioperative use of statins has shown some promise in the prevention of POAF (111,112), and interest in other prophylactic agents has emerged with a large ongoing multicentre trial investigating colchicine (113).

Analgesia and regional anesthesia

Multimodal analgesia, incorporating at a minimum acetaminophen and non-steroidal anti-inflammatories, is an ideal approach for enhanced recovery. Goals include sparing opioids and their side effects, including respiratory depression in a fragile population, while adequately controlling perioperative pain to facilitate mobilization, promote adequate coughing and prevent splinting. Additionally, poorly controlled early acute postoperative pain is known to be predictive of chronic post thoracotomy pain (CPTP) (114). Whether or not more aggressive management of acute pain can actually prevent chronic pain is still debated, with one trial showing that intraoperative use of epidural catheters (as opposed to isolated postoperative use) for thoracotomy reduces the incidence of CPTP (115), however this effect was not confirmed in a later meta-analysis (116).

Many regional techniques can be employed to improve analgesia and reduce opioid consumption post thoracic surgery. These range from fairly short lived (but simple to perform) surgical intercostal blocks and plane blocks such as erector spinae (ESP) or serratus all the way to paravertebral blocks (PVB) and thoracic epidural analgesia (TEA) which are more complex to perform and have more significant risks. In general, the authors reserve epidurals for open thoracotomies, esophagectomies, patients with chronic pain or those at very high risk of PPCs. In a direct comparison, ESP conferred better analgesia and quality of recovery over serratus plane block for minimally invasive thoracic procedures (117). These blocks may also be performed as a rescue in the recovery room for patients who are struggling with pain despite intraoperative intercostal blocks and multimodal analgesia.

A Cochrane review comparing epidural and paravertebral catheters for thoracotomy showed equivalent analgesic efficacy up to 48 hours, with less minor side effects (hypotension, nausea and vomiting, pruritus and urinary retention) in the PVB group (118). Few trials examined analgesic efficacy beyond this timeframe however, and many patients with extensive surgery maintain their neuraxial catheters for longer than 2 days. Another point worth mentioning is the technical difficulty of TEA as evidenced by their higher failure rate, suggesting that not all patients in the TEA arm have an appropriately sited catheter (118). The authors routinely employ epidural waveform analysis which has been demonstrated to decrease the failure rate substantially (119).

Finally, the long-awaited availability of liposomal bupivacaine may have a large impact on the management of thoracic surgical pain. One study showed superior pain control and diminished opioid use extending to the post discharge period with the implementation of an ERAS pathway that included surgical infiltration and intercostal blocks with liposomal bupivacaine and no epidurals even in the thoracotomy population (120).

Surgical technique

Intercostal nerve injury is proposed to play a significant role in the development of CPTP. A small electromyographic study confirmed severely reduced conduction after rib retraction in 90% of patients suggesting traumatic crush injury occurs routinely (121). Strategies that have been employed to mitigate this injury include dissecting an intercostal muscle flap (ICMF) along with the neurovascular bundle to exclude it from retraction and the use of intracostal sutures to protect the nerve in the interspace below the thoracotomy. While some groups have demonstrated a positive impact on postoperative pain with these interventions (122,123), data is inconsistent, particularly with regards to whether addition of the ICMF adds benefit when comparing to intracostal sutures alone (124,125).

Muscle sparing techniques, typically with a more anterior incision and without division of the latissimus dorsi, have been advocated for over traditional posterolateral thoracotomies. Benefits may include improved pain, respiratory mechanics and hospital LOS, as well as preserved options for local flap reconstruction (126-130).

There has been widespread adoption of minimally invasive surgical techniques over the last few decades. The 2013 ACCP guidelines for management of stage I and II non-small cell lung cancer conclude that robust evidence exists for improved short-term outcomes including mortality, a wide range of complications and length of stay, with at least equivalent long-term survival (131). An RCT of patients undergoing lobectomy for stage 1 non-small-cell lung cancer demonstrated much lower pain scores in the first 24 hours post four-port video-assisted thoracoscopic surgery (VATS) approach *vs.* thoracotomy as well as less episodes of moderate to severe pain in the subsequent year (132). Some concerns remain regarding the adequacy of lymphadenectomy achieved with VATS and the treatment of larger tumours. While data from randomized trials is lacking, several observational studies published since the ACCP guidelines support at least the equivalence and in some cases superiority of VATS when compared to thoracotomy even for more locally advanced disease (133-137).

Other novel or non-routine approaches to thoracic surgical procedures are being adopted and researched with increasing interest. These include robotic-assisted lung resections, non-intubated lung surgery and prone esophagectomy, each with their own various purported benefits. So called "non-intubated anesthesia" for lung surgery may range from purely neuraxial techniques with minimal sedation, to regional with sedation but maintaining spontaneous ventilation as well as general anesthesia with a laryngeal mask airway with spontaneous or assisted modes of ventilation. Concerns with these techniques include the potential for hypoventilation or the need to urgently intervene on the airway when in a suboptimal position. A recent meta-analysis comparing an awake spontaneously breathing technique to traditional OLV, although not specific to lung resection, showed several benefits of interest (138). Non-intubated patients had shorter duration of chest drainage, shorter hospital stays, fewer overall and respiratory complications, and improved mortality. In a subgroup analysis for study type, including only RCTs revealed fewer overall and respiratory complications. An in-depth review of all of these novel techniques is beyond the scope of this review but as the body of literature around them increases they may work their way into routine practice.

Chest drain management

Chest drains, while painful and somewhat of a barrier to mobilization, are used in most thoracic cases to prevent pneumothorax, and observe for bleeding and presence of air leak. While interest is emerging in the benefits of chest tube omission for select patients, chest tubes remain the standard of care until larger studies support the safety of this practice and help to identify appropriate patients (139,140). Use of a single chest tube after most thoracic surgeries is preferable unless a more extensive resection is planned such as a bilobectomy (141,142), with one meta-analysis suggesting this decreases pain and length of stay (141). Debate exists regarding whether there is value in placing chest tubes on suction after lung resections. Current evidence generally does not favour the routine application of suction, particularly with regards to duration of chest tube drainage, and there is conflicting evidence with regards to an impact on prolonged air leak (usually defined as lasting 7 days or more) (141-143).

The emerging use of digital drainage devices that can more closely control intrapleural pressures may help clarify this issue with one RCT comparing a pressure of −2 cmH_2O (regulated seal) *vs.* −11 to −20 cmH_2O depending on type of surgery (regulated suction). There was no difference between groups with regards to prolonged air leak or average air leak duration (144).

These devices can enhance early mobilization as they are smaller and don't require wall suction. They can accurately maintain specific intrapleural pressures and quantify the amount of air leak. When compared to traditional systems shorter chest tube duration, length of stay and cost savings are supported by some studies (145,146) and a meta-analysis confirmed these findings as well as a reduction in prolonged air leak (147). Use of portable chest drain systems such as the atrium express mini® can facilitate early discharge in appropriately selected patients who are otherwise ready to go home (148,149).

Less conservative fluid drainage thresholds (300 to 500 mL/day) for chest tube removal have been investigated in some observational and more recently randomized trials. One group demonstrated that increasing fluid criteria to 7 mL/kg/day resulted in no difference in post drain effusion or re-intervention and a shorter length of stay (150). An RCT comparing 150, 300 or 450 mL/day suggested a 300 mL cut off to minimize opioid use and hospital stay but avoid complications as 19.6% of patients in the least conservative group required thoracentesis or chest tube reinsertion for symptomatic effusions (151).

Postoperative mobilization and physiotherapy

Within an ERAS framework for lung cancer resection patients, failure to meet early mobilization targets is predictive of increased length of stay and morbidity within 30 days (152). Immobility is also a well-recognized risk factor for VTE. While bed rest is recognized to be harmful, evidence to support existing mobilization protocols or to define optimal methods is lacking or conflicting (153). Many studies include mobilization in a general ERAS pathway but isolating the effects of this one intervention becomes challenging. Orthostatic hypotension is reported to occur frequently in postoperative thoracic surgical patients, with male gender and presence of an epidural catheter identified as risk factors (154). Teams should be aware of this potential barrier to mobilization and appropriate physiotherapy support should be available to prevent injury.

Incentive spirometry is another routinely used postoperative intervention with little evidence to support its use (155,156). An RCT in thoracotomy patients attempted to define a higher risk subgroup who would benefit, and found a nonsignificant trend to decreased PPCs (157). More robust data is needed to confirm a benefit, but as a low-cost low-risk intervention it remains a part of many ERAS guidelines.

Summary

While the benefits of ERAS pathways observed in other surgical disciplines have also been demonstrated in the thoracic surgical population, there is still a need to better define the roles of individual elements of these pathways. One challenge when assessing the efficacy of the individual components is the amount of heterogeneity in terms of how the interventions are administered (for example GDT means different things in different studies). In some cases, evidence may be lacking but interventions continue to be recommended because of benefit extrapolated from other contexts, or low cost and risk. In other cases, robust evidence for an intervention exists or is emerging, but the specifics of who will most benefit, or how best to apply it, or how long to implement it for, are ongoing areas of research.

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Appendix 1

Case

At the Montreal General Hospital many patients go through our prehabilitation program, typically for a minimum of four weeks, and achieve significant improvement in modifiable risk factors and measurable parameters of fitness [e.g., Duke Activity Status Index (DASI), cardiopulmonary exercise testing (CPET) parameters, HbA1c]. They then proceed with surgery according to our institutional enhanced recovery after surgery (ERAS) pathways starting from a much better baseline than they were before their prehabilitation assessment and program. The following case highlights a different scenario which illustrates how implementation of a prehabilitation program may be used to inform perioperative decision making in challenging patients.

A 79-year-old male patient with a 30-pack year active smoking history presented with a right upper lobe cancer for a video-assisted thoracoscopic surgery (VATS) lobectomy. His medical history was notable for type 2 diabetes on oral agents, coronary artery disease with several stents, atrial fibrillation and hypertension. He had moderate chronic obstructive pulmonary disease (COPD) by gold criteria as well as chronic kidney disease with an estimated glomerular filtration rate (eGFR) of 31 mL/min per 1.73 m^2 and multifactorial anemia. His brain natriuretic peptide levels were 162 pg/mL. He had a 6-minute walk distance of only 210 m and reported a very poor DASI of 10.75. He had lost weight since his diagnosis and had appetite issues. He was deemed to be at very high perioperative risk.

Because of these findings he was referred for prehabilitation prior to surgery. His assessment revealed a predictably low VO_2 peak of 9.9 mL/kg/min and he was severely malnourished as per the patient-generated subjective global assessment (PG-SGA) score. His intervention consisted of a combined aerobic and resistance exercise program along with inspiratory muscle training, increased caloric intake with protein supplementation and intravenous (IV) iron infusion.

Unfortunately, despite participating in the program, on reassessment this patient did not demonstrate an improvement. This information was reviewed with the interdisciplinary team including surgery, oncology, anesthesia and of course the patient and their family, leading to the decision to proceed with stereotactic body radiotherapy as an alternative to lung resection in this patient. While the goal of prehabilitation is to improve perioperative outcomes, this case highlights how the thorough assessment and response to prehabilitation can also be used to inform decisions about patient care trajectories.

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