Original Article

Implementation of an enhanced recovery after thoracic surgery care pathway for thoracotomy patients—achieving better pain control with less (schedule II) opioid utilization

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Background: Enhanced recovery after surgery protocols incorporate evidence-based practices of pre-, intra- and post-operative care to achieve the most optimal surgical outcome, safe on-time discharge, and surgical cost efficiency. Such protocols have been adapted for specialty-specific needs and are implemented by a variety of surgical disciplines including general thoracic surgery. This study aims to evaluate the impact of our enhanced recovery after thoracic surgery (ERATS) protocol on postoperative outcomes, pain, and opioid utilization following thoracotomy.

Methods: This is a retrospective analysis of patients undergoing elective resection of intrathoracic neoplasms via posterolateral thoracotomy between 1/1/2016 and 3/1/2020. Our enhanced recovery protocol, with a focus on multimodal pain management (opioid-sparing analgesics, infiltration of local anesthetics into intercostal spaces and surgical wounds, and elimination of thoracic epidural analgesia) was initiated on 2/1/2018. Demographics, clinicopathology data, subjective pain levels, peri-operative outcomes, in-hospital and post-discharge opioid utilization were obtained from the electronic medical record.

Results: A total of 98 patients (43 pre- and 55 post-protocol implementation) were included in this study. There was no difference in perioperative outcomes or percentage of opioid utilization between the two cohorts. The enhanced recovery group had significantly less acute pain. A significant reduction of in-hospital potent schedule II opioid use was noted following ERATS implementation [average MME: 10.5 (3.5–16.5) (ERATS) *vs.* 19.5 (12.6–36.0) (pre-ERATS), P<0.0001]. More importantly, a drastic reduction of total and schedule II opioids dispensed at discharge was noted in the ERATS group [total MME: 150 (100.0–330.0) *vs.* 800.0 (450.0–975.0), P<0.0001 and schedule II MME: 90.0 (0–242.2) *vs.* 800.0 (450.0–975.0), P<0.0001; ERATS *vs.* pre-ERATS respectively]. A shorter hospital stay (median difference of 1 day, P=0.0012 and a mean difference of 2.4 days, P=0.0054) was observed in the enhanced recovery group.

Conclusions: Implementation of an enhanced recovery protocol for thoracotomy patients is safe and associated with elimination of thoracic epidural analgesia, decreased postoperative pain, shorter hospitalization, drastic reduction of post-discharge opioid dispensed and decreased dependence on addiction-prone schedule II narcotics.

Keywords: Thoracotomy; post-operative pain; post-operative opioid utilization; enhanced recovery after thoracic surgery (ERATS)

Submitted Mar 29, 2021. Accepted for publication May 20, 2021.
doi: 10.21037/jtd-21-552
View this article at: http://dx.doi.org/10.21037/jtd-21-552

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Introduction

Enhanced recovery after thoracic surgery (ERATS) protocols have gained significant traction in the past 5 years (1-5). Keeping the essential components of ERAS®, as initially described in early 2000's and with adaptations over time (6), ERATS protocols have been developed for thoracic surgical patients. ERATS incorporates all nuances associated with the care of patients undergoing intrathoracic procedures, either by thoracotomy or by minimally invasive thoracoscopic surgery (MITS: video-assisted or robotic thoracoscopy) (7). Patients undergoing thoracic surgery are frequently elderly individuals with significant cardiopulmonary and metabolic comorbidities (8). Postoperative pain is intrinsic to thoracic surgical procedures, and pulmonary impairment following lung resections, together with underlying co-morbidities have a strong impact on post-operative outcomes. While the components of ERATS work synergistically to provide the most optimal outcomes, effective thoracic pain control with an opioid-sparing strategy, coupled with posterior intercostal nerve blocks and surgical wound infiltration with long-acting local anesthetic preparation liposomal bupivacaine, plays an essential role. Since the initial reports by Rice and Mehran of the MD Anderson Cancer Center (9,10) that described and popularized this technique within the context of ERATS, many medical centers, including our own, have described successful implementation of ERATS with significant improvement of a wide range of outcome metrics such as reduced pain and opioid requirements, postoperative complications, and postoperative hospital length of stay (LOS) (1,2,11-13).

Reduction of postoperative pain and opioid requirements in thoracic patients has been associated with decreased postoperative complications, particularly cardiopulmonary complications, and decreased hospital LOS in those undergoing thoracotomies for pulmonary resections (1,2,11,12). It has been argued that MITS, in and of itself, is a component of ERATS (5) and it is hard to improve already optimal outcome metrics such as postoperative LOS of MITS. Within the context of a well-implemented ERATS program, Krebs and colleagues have demonstrated equivalent short-term outcomes (LOS, complication rates, postoperative pain scores) of patients undergoing pulmonary lobectomy either by MITS or thoracotomy approaches (11). The most important effect of ERATS is the ability to reduce both in-hospital and post-discharge opioid requirements while maintaining adequate pain control (2,12,13). Exposure to potent opioids (those classified as schedule II by the FDA such as morphine, oxycodone, hydromorphone) increases the risk of dependency (14,15) and if made available outside the hospital setting would increase the risk of inappropriate use, especially in the current setting of the opioid crisis in the United States (16-19).

We implemented ERATS at our medical center on 2/1/2018 for all patients undergoing thoracic surgical procedures. This study aims to assess the safety of ERATS protocol implementation and the effect of ERATS on mitigating postoperative pain, reducing opioid requirements, and evaluating short-term clinical outcomes of patients undergoing lung resection by thoracotomy until 3/1/2020, using a comparable cohort of pre-ERATS patients as historical controls.

The study was conducted and reported in concordance with the Strengthening the Reporting of Observational Studies in Epidemiology STROBE reporting checklist (20) (available at http://dx.doi.org/10.21037/jtd-21-552).

Methods

Patient population

A retrospective analysis of data extracted from our prospectively maintained thoracic surgery database and the electronic medical record EPIC® of patients at University of Miami Hospital was performed following institutional review board approval with a waiver of patient consent requirement (IRB: 20180827). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Patients undergoing posterolateral thoracotomy between 01/01/2016 and 3/1/2020 were reviewed. All adult patients (≥18 years old) undergoing same-day admit elective pulmonary procedures (anatomic resection—segmentectomy, simple or bronchoplastic sleeve lobectomy, bilobectomy, pneumonectomy or non-anatomic sublobar wedge resections, the majority of which included intrathoracic lymphadenectomy for oncologic indications) or mediastinal-pleural procedures (resection of mediastinal tumors—mainly complex thymic neoplasms or pleural pathology such as fibrous tumor of pleura) via serratus anterior- and latissimus dorsi-sparing postero-lateral thoracotomy approach for curative-intent resections of intrathoracic neoplasms were included. Patients in whom accurate assessment of postoperative pain and narcotic use was not feasible such as those who remained on endotracheal intubation/mechanical

ventilation following thoracotomy and those with long-term opioid use for chronic pain (determined by clinical history of taking scheduled opioid analgesics for at least 2 months immediately preceding thoracic procedures) were excluded. Patients who had sternotomy, clamshell, or hemi-clamshell incisions, radical pleurectomy for primary or secondary pleural cancers, chest wall resections, esophageal procedures, or pleuro-pulmonary decortication for empyema were also excluded. We implemented our ERATS protocol (Table S1) on 2/1/2018 for all thoracic surgical patients who underwent either robotic thoracoscopy or thoracotomy. The thoracotomy patient cohort prior to this date (pre-ERATS group: 1/1/2016 to 1/31/2018) served as historical control for the ERATS patients (2/1/2018 to 3/1/2020).

Development and Implementation of ERATS.

Our ERATS care protocol (Table S1) encompasses all aspects of pre-, peri-, intra- and post-operative management of thoracic surgical patients, similar to previously published protocols (1-7). Prior to formal implementation of ERATS, many of these care components were part of our routine practice but not uniform amongst various providers. Thoracic epidural analgesia was the main component of acute postoperative pain control supplemented by oral or intravenous schedule II opioids (morphine, oxycodone, and hydromorphone) for breakthrough pain prior to ERATS. Thoracic epidural catheters were placed prior to the induction of anesthesia and managed by the regional anesthesia team. Epidural analgesia typically was initiated at the end of the case with baseline infusion of bupivacaine with or without an opioid such as fentanyl or hydromorphone. The initial settings of epidural analgesia were routinely a basal infusion rate titrated to achieve optimal pain control and to avoid hypotension and a patient-control administration (PCA) option. It was typically removed one day after discontinuation of the chest tube. Other non-opioid analgesics (acetaminophen, tramadol, ketorolac, and ibuprofen) were used sparingly. The exact quantity and formulations of opioids used varied greatly based on the patients' need and the providers' discretion. One critical element of our ERATS implementation is our multimodal opioid (schedule II)-sparing pain management strategy coupled with the off-label use of liposomal bupivacaine (LipoB) (Exparel®, Pacira Pharmaceuticals Inc., Parsippany, NJ) for a single-dose intercostal nerve block and surgical wound infiltration to achieve durable regional analgesia up to 4 days. Moreover, ERATS patients received scheduled administration of acetaminophen, gabapentin, ibuprofen, or ketorolac (in the absence of contraindications such as renal dysfunction, high sanguineous chest tube drainage in the immediate postoperative period or known intolerance to NSAIDs) and the schedule IV opioid tramadol. Nursing staff in the pre-operative clinic, post-anesthesia care unit and thoracic surgery unit, as well as the operating room anesthesia staff, all received proper in-service ERATS training prior to implementation. The thoracic surgery unit nursing staff was regularly provided extensive in-service training regarding all components of the postoperative care, pain assessment and administration of PRN opioid analgesics commensurate to patient-reported pain levels. For intraoperative regional analgesia, LipoB was diluted with 50 mL of injectable saline and the initial 30 mL was used to infiltrate the sub-dermis of the entire intended thoracotomy prior to skin incision, upon entrance into the pleural cavity and the remaining 40 mL of the mixture was used to infiltrate 9 intercostal spaces as well as the soft tissue at the posterior thoracotomy site above and below the incision, similar to the technique described by Mehran and colleagues under direct vision using a 21 gauge spinal needle (9,10). The nursing staff routinely performed scheduled objective pain assessments using the visual analog pain scale and administered rescue opioid analgesics (as prescribed) at their discretion. During the initial 6-month transition period following the launch of our ERATS program, clinical compliance by all healthcare providers was closely monitored and enforced. We routinely evaluated in-hospital pain levels and opioids required by patients throughout the ERATS implementation phase and tailored our post-discharge opioids prescription practices over time.

Data collection and outcome metric measurements

Outcomes

Safety outcomes were overall postoperative complications and 90-day mortality. Efficacy outcomes were post-operative pain, hospital length of stay, and in-hospital and post-discharge opioid utilization.

Data source and description

The thoracic surgery database prospectively collects detailed clinical parameters, including but not limiting to patient demographics, comorbidities, pulmonary function tests, body mass index (BMI), operative details,

pathologic diagnoses, AJCC 8th edition pathologic TNM staging for primary lung cancer, 90-day postoperative complications (using the Clavien-Dindo classification) (21) and hospital LOS in days, as well as postoperative re-admission incidence. The database is maintained by a nurse practitioner and regularly audited for accuracy by the surgical faculty (DMN).

Data attributes

The following parameters were extracted from the hospital electronic medical record: patient-reported pain scores (scores were averaged over a 24-hour period and recorded up to 4 postoperative days), in-hospital analgesics dispensed (opioids: oxycodone, hydromorphone, morphine, fentanyl, tramadol; non-opioids: acetaminophen, gabapentin, ketorolac, ibuprofen, celecoxib, bupivacaine, lidocaine, liposomal bupivacaine). The quantities of opioids dispensed are expressed as p.o. morphine milligram equivalent (MME). Information regarding post-discharge re-admissions, either to our hospital or to another healthcare facility, were obtained from EPIC® and also via post-discharge telephone follow-ups and clinic visits. Post-discharge analgesics including types and dosage of opioids prescribed were collected from the discharge summary. The filling and refilling (within 30-day after discharge) of all types of opioids were monitored by reviewing EPIC® data and by routine surveying of our patients during telephone follow-ups by our advanced registered nurse practitioner and by the attending surgeons at postoperative clinic visits. Such independently obtained information was frequently cross-referenced for accuracy. As EPIC® was implemented on 1/2017 at our institution, reliable data on post-discharge opioid utilization were available only for 27 patients in the second half of the pre-ERATS period (1/1/2017 to 1/31/2018).

Statistical analysis

Statistical analysis of categorical variables, expressed as percentages and frequencies, were analyzed using either Chi-square or Fisher's exact test as appropriate. Continuous variables were expressed as median and interquartile range and compared using a Student's *t*-test, an unequal variance *t*-test, or a Mann-Whitney U test as appropriate (22). Univariable and multivariable linear, low-rank splines and logistic regression models were used to measure primary end-point outcomes. The low-rank regression splines were specified in the framework of generalized additive models and fitted to penalized likelihood estimation (GAMPL in SAS) to produce flexible nonparametric regressions and assess the relationship of ERATS on the total length of stay. The 95% confidence intervals were reported in the parametric models. In multivariable models, we adjusted for age, sex, and BMI. Mixed linear model test was used to analyze post-operative pain scores up to postoperative day 4. We assumed linear time trends, giving rise to the intercept (initial pain at Day 0) and the slope (rate of change in pain per day on study) estimates. Then we used least squares means at each time point. Statistical analysis was performed with SAS software, version 9.4 (SAS Institute, Cary NC). A 2-sided P value of ≤0.05 denotes statistical significance.

Results

A total of 98 patients (43 in the pre-ERATS period and 55 after ERATS implementation) met the selection criteria and were included in our analysis. Patient demographics and clinical characteristics of the two cohorts were similar (*Table 1*). In patients with primary lung cancers, nearly 50% had locally advanced stage 3A/B or stage 4 cancer (3 cases due to unsuspected microscopic pleural metastasis). Similar numbers of patients in either cohort had induction chemotherapy for known pre-resection mediastinal N2 lymph node metastasis. All patients with primary lung cancer had anatomic lung resection and mediastinal lymphadenectomy. Similar incidences of other intrathoracic cancers (secondary lung cancers or other neoplasms: invasive thymoma, malignant solitary fibrous tumor of pleura) were noted in either group. There was no difference in estimated intraoperative blood loss or duration of operating room time between the two cohorts. All cases were staffed by either of the two attending surgeons (DMN, NV).

Regarding safety outcomes, there was no statistically significant difference in the overall incidence of complications (pre-ERATS: 37.2% *vs.* ERATS: 25.5%) between the two groups (P>0.05) (*Tables 2,3*). Fewer pulmonary complications, however, were observed in ERATS patients. There was no 90-day mortality. Regarding the efficacy outcomes, ERATS was associated with a significant reduction of postoperative LOS (in days) [pre-ERATS of 5.0 (4.0–7.0) and 6.5 (4.3) *vs.* ERATS of 4.0 (3.0–6.0) and 4.4 (2.0), median (IQR) and mean (SD), P=0.0012 and P=0.0054 respectively] both in univariable (Estimate =–0.375; P<0.001) and multivariable analysis (–1.94; P=0.003) which was adjusted for patient age, gender,

Table 1 Demographics, clinical characteristics of all patients

Patient and operative characteristics	Overall (n=98)	Pre-ERATS (n=43)	ERATS (n=55)	P value
Demographics				
Age, median (IQR)	68.0 (58.5–73.5)	68.0 (60.0–73.5)	65.0 (57.0–73.2)	0.3280
Gender (M:F)	54:44	26:17	28:27	0.3453
ASA, median (IQR)	3 (3–3)	3 (3–3)	3 (3–3)	
BMI (kg/m^2), median (IQR)	26.5 (24.3–29.8)	25.9 (22.7–28.2)	26.6 (23.2–30.7)	0.51
FEV1 (% normal), median (IQR)	74.0 (60.5–87.5)	68.5 (55.2–82.7)	74.5 (62.7–93)	0.40
DLCO (% normal), median (IQR)	72.5 (62.0–84.5)	70.0 (62.0–79.0)	73.0 (60.0–85.7)	0.08
Clinical characteristics				
Primary lung cancer, n (%)	74 (75.5)	35 (81.4)	39 (70.9)	0.25
Pathologic stage 0–2	38 (51.3)	19 (54.3)	19 (48.7)	0.65
Pathologic stage 3A-4	36 (48.6)	16 (45.7)	20 (51.3)	
Induction therapy	9 (12.1)	4 (11.4)	5 (12.8)	
Secondary lung cancer and other neoplasms, n (%)	24 (25.5)	8 (18.6)	16 (29.1)	0.25
Anatomic resections, n (%)	83 (84.7)	40 (93.0)	43 (78.2)	0.051
Wedge and other resections, n (%)	15 (15.3)	3 (7.0)	12 (21.8)	
Estimated blood loss (mL)	100.0 (80.0–175.0)	100.0 (100.0–200.0)	100.0 (100.0–200.0)	0.82
Operating time (min)	270.0 (240.0–314.5)	260.0 (240.0–298.0)	292.0 (212.0–387.5)	0.42

ERATS, enhanced recovery after thoracic surgery; IQR, interquartile range; BMI, body mass index.

and BMI (*Tables 2*,*3*).

Patients in the ERATS group reported significantly less pain than the pre-ERATS cohort as shown in *Figure 1* (P<0.0001). Despite the significant difference of baseline pain measurement (Estimate at time 0 =–1.5021; P=0.0003) decreased patient-reported pain scores were significantly different between and within groups at 24, 48, 36, 64 hours after surgery: respective estimates =–1.8635, P<0.0001; –1.9009, P<0.0001; –2.6871, P<0.0001; –2.5093, P<0.0001. None of ERATS patients *vs.* 36 of 43 pre-ERATS patients received thoracic epidural analgesia (P<0.00001). The other 7 pre-ERATS patients had other forms of postoperative pain management (patient-controlled analgesia with intravenous opioids and/or intercostal nerve blocks with local anesthetic agents) due to patient refusals or unsuccessful insertion of the catheter.

The use of acetaminophen and NSAIDs was similar between both groups while 95% of ERATS patients received gabapentin *vs.* 16% in pre-ERATS cohort (P<0.00001) (*Table 4*). In-hospital opioid utilization was similar in both groups even in the absence of thoracic epidural analgesia in the ERATS patients (*Figure 2A*). A 2-fold decrease in schedule II opioid use was observed in ERATS patients [ERATS daily average MME median (IQR): 10.5 (3.5–16.9) *vs.* pre-ERATS daily average MME median (IQR): 19.5 (12.6–36.0), P<0.0001] (*Figure 2A*), which was coupled with more schedule IV opioid tramadol use for postoperative analgesia (*Table 4*, *Figure 2A*). More importantly, ERATS was associated with a 5-fold reduction of post-discharge opioid prescribed [pre-ERATS total MME: 800.0 (450.0–975.0) *vs.* ERATS total MME: 150.0 (100.0–330.0), P<0.0001]. Notably there was a 10-fold reduction of schedule II opioids prescribed for patients of the ERATS cohort [pre-ERATS MME: 800.0 (450.0–975.0) *vs.* ERATS MME: 90.0 (0–242.2), P<0.0001]. Similar to the in-hospital opioid utilization profile, more tramadol was prescribed at discharge for patients in the ERATS group (*Figure 2B*). There was a significant reduction in the incidence of both initial filling and re-filling of schedule II opioids after discharge in ERATS patients (*Table 4*). For instance, 78% of ERATS patients filled their schedule II initial prescription *vs.* 100% of pre-ERATS patients

Table 2 Post-operative outcomes

Post-operative outcome	Pre-ERATS (n=43)	ERATS (n=55)	P value
90-day mortality	0	0	
Hospital LOS [median (IQR); mean (SD)]	5.0 (4.0–7.0); 6.5 (4.3)	4.0 (3.0–6.0); 4.4 (2.0)	0.0012; 0.0054
Post-operative outcomes			
Complications (Clavien-Dindo), n (%)[#]			
0	27 (62.8)	41 (74.5)	0.27
1–2	8	9	
3–4	8	5	
5	0	0	
Cardiovascular	3	5	1.00
atrial fibrillation	2	1	
acute coronary syndrome	0	0	
TEA-induced hypotension/ICU	1	0	
Pulmonary	12	6	0.038
Respiratory insufficiency requiring mechanical ventilation	4	2	
Fiberoptic bronchoscopy for atelectasis/pneumonia	4	2	
Bronchopleural fistula/empyema	1	0	
Chest tube re-insertion (pneumothorax/subcutaneous emphysema)	2	0	
Air-leak >5 days	1	2	
Gastro-intestinal/genito-urinary	4	3	1.00
Ileus	1	1	
Acute kidney injury	2	1	
Urinary retention	1	1	
Others (FUO, confusion, vocal cord paralysis, transfusion)	3	4	
Re-operations	0	2	0.50
Re-admissions, n (%)	6 (13.9)	2 (3.6)	0.13

[#], highest score of multiple complications. ERATS, enhanced recovery after thoracic surgery; LOS, length of stay; IQR, interquartile range; SD, standard deviation; ICU, intensive care unit; FUO, fever of unknown origin.

(P=0.0065). Only 17.2% of ERATS patients needed a refill of their opioid prescription *vs.* 40.7% of the pre-ERATS cohorts (P=0.034) and only 50% of those refills were schedule II *vs.* 100% of refills for pre-ERATS patients were scheduled II opioids (P=0.012).

Discussion

Our retrospective analysis demonstrated that ERATS implementation for patients undergoing posterolateral thoracotomy for curative-intent resection of intrathoracic neoplasms was safe, efficacious, and associated with significantly less acute postoperative pain. It also leads to complete elimination of thoracic epidural analgesia alongside its potential adverse side effects (23,24), without increasing in-hospital opioid requirements. Most importantly it allowed for a drastic reduction of post-discharge opioid utilization. A notable observation is

Table 3 Univariate and multivariate analysis of outcomes including complications, length of stay and prolonged length of stay

Pain scores (over 4 post-operative days)	Estimate/OR (95% CI)	P value
ERATS *vs.* pre-ERATS, estimate (95% CI)	−2.51 (−3.4646, −1.5540)	<0.0001
Post-operative complications, OR (95% CI)		
Univariable: ERATS *vs.* pre-ERATS	0.574 (0.245, 1.345)	0.2009
Multivariable		
ERATS *vs.* pre-ERATS	0.558 (0.227, 1.372)	0.2035
Age	1.037 (0.995, 1.081)	0.0869
Male *vs.* female (reference)	0.99 (0.387, 2.528)	0.9825
BMI	1.1 (1.018, 1.188)	0.0161
LOS (continuous non-normal outcome) (estimate)		
Univariable: ERATS *vs.* pre-ERATS (reference)	−0.375	0.0005
Multivariable		
ERATS *vs.* pre-ERATS (reference)	−1.942	0.0034
Age	6.098	0.2464
Male *vs.* female (reference)	−0.215	0.7518
BMI	2.211	0.5427

ERATS, enhanced recovery after thoracic surgery; LOS, length of stay; BMI, body mass index.

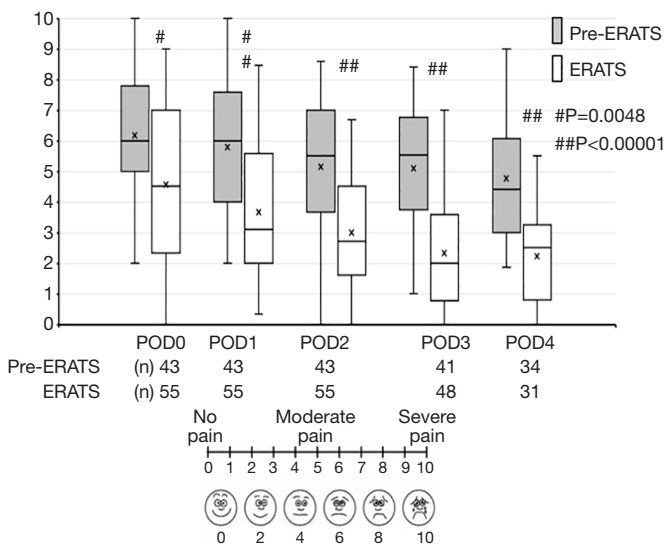

Figure 1 Significant reduction of postoperative pain in ERATS patients. Postoperative patient-reported subjective pain scores before and after implementation of ERATS in thoracotomy patients using the visual analog pain scale (0: no pain to 10: worst pain possible). Daily pain scores are expressed using the box-whisker plots (box: IQR, –: median, x: mean, minimal and maximal values and outliers) over multiple postoperative days (POD) for each group. n represents the number of subjects per group for that particular POD. A mixed effects model analysis revealed significant individual differences in post-operative pain trajectory slopes.

Table 4 Post-thoracotomy in-hospital and post-discharge analgesic utilization

Analgesic management	Pre ERATS (n=43)	ERATS (n=55)	P value
Thoracic epidural	36	0	<0.0001
9-level Intercostal nerve block/wound infiltration with Liposomal bupivacaine	0	55	
Other methods of postoperative pain management (nerve blocks; intravenous opioid PCA)	7 (4; 3)	2 (PCA)	
In-hospital opioid use (average daily MME), median (IQR)	17.5 (12.8–29.3)	23.8 (16.7–35.2)	0.19
Schedule II opioid use, n (%)	43/43 (100%)	53/55 (91.4%)	0.50
Schedule IV opioid use, n (%)	1/43 (2.3%)	52/55 (94.8%)	<0.0001
Non-opioid analgesics, n (%)			
Acetaminophen	40/43 (93.0%)[#]	52/55 (94.5%)*	1.00
NSAIDs	22/43 (51.1%)[##]	29/55 (52.7%)[##]	1.00
Gabapentin	7/43 (16.3%)	52/55 (94.5%)	<0.0001
Discharge opioid use (MME), median (IQR)[###]	800.0 (450.0–975.0)	150.0 (110.0–347.0)	<0.0001
Incidences, n (%)			
Opioid prescription filled	27/27 (100%)	50/55 (90.9%)	0.16
Schedule II opioid	27/27 (100%)	39/50 (78.0%)	0.0065
Schedule IV opioid	1/27 (3.7%)	49/50 (98.0%)	<0.0001
Opioid prescription refilled	11/27 (40.7%)	10/55 (17.2%)	0.034
Schedule II opioid	11/11 (100%)	5/10 (50.0%)	0.012
Schedule IV opioid	2/11 (18.2%)	5/10 (50.0%)	0.18
Non-opioid analgesics prescribed, n (%)			
Acetaminophen	38/43 (88.4%)	55/55 (100%)	0.014
Gabapentin	10/43 (23.2%)	50/55 (90.9%)	<0.0001
NSAIDs	11/43 (25.5%)	33/55 (60.0%)	0.001

[#], as part of oxycodone-acetaminophen PRN; [##], ibuprofen or ketorolac; *, scheduled acetaminophen; [###], only available for 27 pre-ERATS patients. ERATS, enhanced recovery after thoracic surgery; PCA, patient-controlled analgesia; MME, morphine milligram equivalent; IQR, interquartile range.

the ability of ERATS to decrease a reliance on schedule II opioids both in-hospital and after discharge for pain management. Our study also provided a granular quantitative analysis of post-discharge opioid utilization (total amount and subtypes of opioid prescribed and incidence of fill and refill of narcotic prescriptions), a feature not previously reported. Moreover, ERATS was also associated with a statistically significant reduction of hospital LOS in general and for prolonged LOS hospital courses.

Our study was able to shed light on the impact of ERATS for three main metrics: (I) clinical outcomes including hospital LOS, (II) patient-reported subjective pain levels and (III) opioid prescription (particularly schedule II narcotics) requirements. Before the formal implementation of ERATS at our institution, many prophylactic measures had already been instituted to minimize postoperative gastrointestinal, genitourinary, and cardiopulmonary complications. This resulted in little difference (except for a clear reduction of pulmonary adverse events) in the rate of postoperative complications between two patient cohorts. The ERATS patients however had a shorter hospital LOS that was attributable to better pain control, early ambulation, timely removal of tubes and drains, and patients

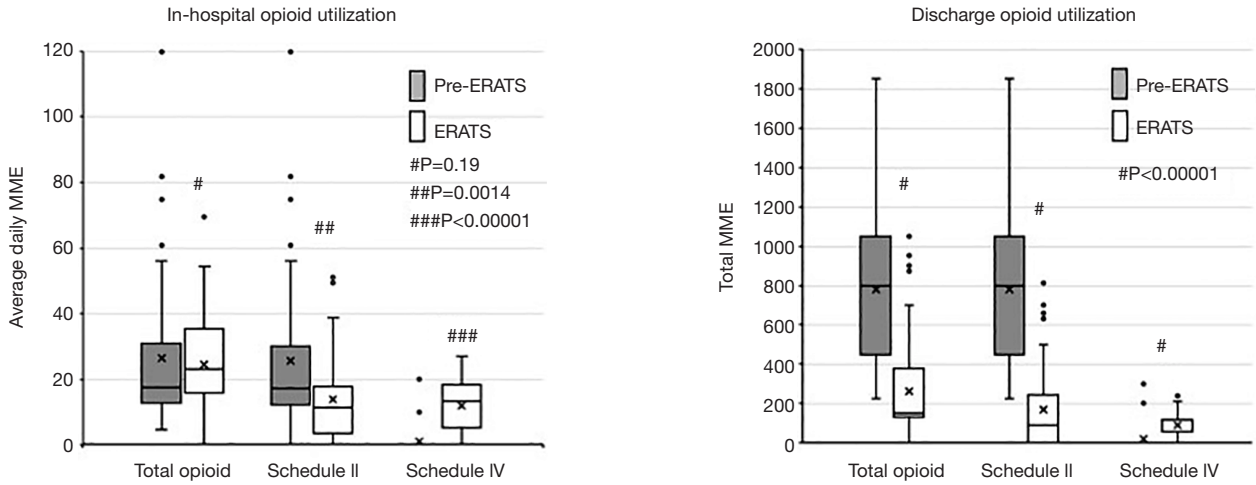

Figure 2 In-hospital and post-discharge opioid dispenses before and after implementation of ERATS in thoracotomy patients, expressed as average daily MME (calculated by dividing total MME of entire hospital stay with number of postoperative days in hospital) for in-hospital opioid use (A) and total MME for post discharge opioid prescription (B) using the box-whisker plots. While there was no difference in the total in-hospital opioid utilization between the two cohorts, a 2-fold reduction of schedule II opioid and increased tramadol use was seen in ERATS patients. There was a 5-fold and 10-fold reduction of total opioid and schedule II opioid prescribed for ERATS patients at discharge from the hospital (B). Pairwise statistical analysis was performed using Mann-Whitney U test. ERATS, enhanced recovery after thoracic surgery; MME, morphine milligram equivalent.

clinically and psychologically ready to be discharged. Our findings recapitulated previously described salutary results of ERATS. Van Haren and colleagues from MD Anderson Cancer Center (Houston, TX) reported in a large patient cohort over an 11-year period (1/1/2006-12/31/2016) significant reduction of cardio-pulmonary complications and hospital LOS following ERATS implementation in thoracotomy patients (1). In a more contemporary dataset (2015 to 2017), Martin and colleagues from the University of Virginia (Charlottesville, VA) reported that ERATS was associated with a significant reduction of hospital LOS but no changes in post-thoracotomy complications (except for reduction of postoperative atelectasis) (2). Going beyond these initial observations, Krebs and colleagues further demonstrated that, after risk-adjustment and within the context of a well-applied ERATS program, there was no difference in postoperative pain, opioid use, complication rates or hospital LOS between patients undergoing lobectomy for lung cancer either by thoracotomy or video-assisted thoracoscopy (11). Our own data presented here and previously published for ERATS in robotic thoracoscopic patients (13) certainly supports this notion even though we have not formally performed such comparative analysis. Since its establishment, our ERATS protocol for thoracotomy has served our patients well.

We noticed that safe elimination of the use of thoracic epidural analgesia simplified care for these thoracotomy patients. The surgical team now has total control of the pain management with real-time assessment of postoperative pain level and can effectively address patients' analgesic needs. The highlight of ERATS is the combination of intercostal nerve blocks with liposomal bupivacaine, multiple non-opioid analgesics of different mechanisms of action, and tramadol, a schedule IV opioid, to achieve effective pain control and to mitigate reliance on potent, addiction-prone schedule II opioids such as morphine, oxycodone, or hydromorphone. In fact, as shown in *Figure 1*, ERATS patients without thoracic epidural analgesia had significantly less pain than pre-ERATS patients. While being an effective analgesic, NSAIDs (either ketorolac or ibuprofen) could only be given in about 50% to 60% of our patients due to clinical or pharmacological contra-indications. A significant amount of opioids prescribed at hospital discharge, particularly schedule II narcotics, in the pre-ERATS cohort reflected an outdated prescribing practice, which did not exploit the use of schedule IV opioid tramadol and non-opioid analgesics and also likely represented over-prescription. Pre-ERATS patients routinely received discharge prescriptions of 14-day supply oxycodone/acetaminophen (5/325; 1 to 2 tablets

Q6hrs PRN or 420 to 840 MME). ERATS patients were discharged with amounts and types of opioids based on their postoperative pain levels and in-hospital opioid needs together with all other non-opioid analgesics, achieving a much lower post-discharge MME similar to practice patterns for general surgical patients (25,26) and thoracic patients (27). Over-prescription of opioids for postoperative patients is a well-recognized phenomenon (18,25,26). This was mitigated following ERATS implementation. The low MME and reduced incidence of opioid (particularly schedule II) refills by patients indicated that their pain was adequately controlled and they were not denied of adequate opioid analgesics at the time of discharge from the hospital. Decreased early postoperative pain in ERATS patients correlated with fewer out-of-hospital opioid needs (a surrogate of pain levels), a notion compatible with the previous observation by Katz *et al.* in a landmark study in 1996 demonstrating early postoperative pain intensity was linked to development of persistent postoperative pain and possible persistent opioid use (28,29). Our study focuses on acute post-thoracotomy pain and short-term use of opioids, particularly potent schedule II narcotics, and not on long-term persistent pain and chronic opioid use following after thoracotomy. Reduction of postoperative schedule II opioid use has many salutary effects including decreased drug exposure leading to lower risk of dependence/addiction, less availability of opioids in the community and reducing the opportunity for inappropriate use/abuse particularly in this current opioid epidemic in the USA. To put this in a broader context, in a study by Chen *et al.* of 18,343 patients, 46% were prescribed opioids at hospital discharge. There was a trend of 36% over prescription in the thoracic service (30), demonstrating the concerning role of health care professionals in contributing to the opioid pandemic, particularly since the surplus medication following surgery is the primary source of prescription diversion. Thus, it is imperative to understand how we can limit opioid use within the healthcare system while providing optimal outcomes.

This study has many limitations. It is a single-institution retrospective longitudinal case series analysis of a before-and-after nature that carries intrinsic biases. The study also suffers from the small sample size despite attempts to extend the study for more than four years around the ERATS initiation date. This population represented about half of our open cases over the study period. We perform most of our thoracic procedures for lung cancer using robot-assisted thoracoscopy and reserve a thoracotomy approach for complex lung resections. Another limitation is our inability to complete the post-discharge MME for the first half of the pre-ERATS cohort but there is no reason to believe that these patients would have been given prescriptions for a much different amount of opioids (higher or lower) at the time of discharge. These limitations, however, would not diminish the significance of our observations on the salutary effects of ERATS in thoracotomy patients.

In conclusion, this retrospective analysis highlights many positive impacts of ERATS implementation on patients undergoing thoracotomy for pulmonary resection. Notably there is a reduction of hospital LOS, postoperative pain and decreased reliance on opioids, particularly schedule II class of narcotics, for adequate acute postoperative pain management. This ERATS protocol is now the standard of care for our thoracic patients.

Acknowledgments

The University of Miami supported this work.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jtd-21-552

Data Sharing Statement: Available at http://dx.doi.org/10.21037/jtd-21-552

Peer Review File: Available at http://dx.doi.org/10.21037/jtd-21-552

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-21-552). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was performed following institutional review board approval with a waiver of patient consent requirement (IRB: 20180827). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Kodia K, Stephens-McDonnough JA, Alnajar A, Villamizar NR, Nguyen DM. Implementation of an enhanced recovery after thoracic surgery care pathway for thoracotomy patients—achieving better pain control with less (schedule II) opioid utilization. J Thorac Dis 2021;13(7):3948-3959. doi: 10.21037/jtd-21-552

Supplementary

Table S1 Components of ERATS protocol at the University of Miami

Preoperative consultation
Extensive counseling of patients and family members about operative plans
Realistic expectation of postoperative recovery & multimodal pain management
Printed information booklet with instructions
Preoperative clinic visit
Complete review of medical & anesthesia history
Preoperative clearance
Routine preoperative instructions
2 bottles of carbohydrate drinks, 2 hours before surgery
Perioperative care
Acetaminophen 1,000 mg (1 hour prior to surgery)
Gabapentin 100 mg (1 hour prior to surgery)
Prophylactic antibiotics (Cefazolin 2 gm for <120 kg or 3 gm >120 kg; Vancomycin 1,000 mg for penicillin allergy)
Anesthesia care: patient directed fluid management, anti-emetics
Intercostal nerve blocks and infiltration of surgical wounds with local anesthetics with liposomal bupivacaine
Postoperative care
Analgesics
Acetaminophen 1000 mg per os (PO) Q (every) 8h
Tramadol 50 mg PO Q6h
Ibuprofen 600 mg PO Q8h post-operatively or Toradol 15 mg Q6h IV PRN for 2 days (if no medical contraindications) timing of first dose at the discretion of the attending surgeon
Gabapentin 100 mg PO Q8h
Oxycodone 5 mg PO Q6h as needed (PRN) (pain scale: 4–6)
Oxycodone 10 mg PO Q6h PRN (pain scale: 7–10)
Morphine 2 to 4 mg IV Q6h PRN or Hydromorphone 0.5–1.0 mg IV or 2–4 mg p.o. Q6h PRN for breakthrough pain
Heparin 5,000 U subcutaneous Q8h
Metoprolol 12.5 mg Q12h (if not already on a beta-blocker following anatomic resections)
Tamsulosin 0.4 mg daily (>50 years old)
Bowel regimen (Colace & Dulcolax scheduled; Miralax & Milk of magnesia PRN)
Incentive spirometer & ambulation on POD 0
Regular diet on postoperative day 1
Assessment for home oxygen requirement (to prevent discharge delays)
Chest tube removal (postoperative day (POD) 1–2, when volume <5 mL/kg/day)
Foley catheter removal (POD 2)
Intravenous fluid 1 mL/kg until voiding
Discharge plan
Verbal & printed discharge instructions
Contact ARNP or physician's office for advice and management of excessive neuropathic pain
Post-discharge analgesics
Acetaminophen 1,000 mg PO Q8 h for 20 days
Tramadol 50 mg PO Q6h for 3 days (12 tablets; if used postoperatively in-hospital)
Gabapentin 100 mg PO Q8 h for 60 days (30 days supply refill ×1); titrating up to address post-discharge neurogenic pain
Ibuprofen 600 mg PO Q8h for 20 days
Oxycodone 5 mg PO Q6 h PRN for 3 days (12 tablets; if used postoperatively in-hospital)
Pantoprazole 40 mg PO daily for 20 days

PO, per os; IV, intravenous; POD, post-operative day; PRN, as needed; Q, every; h, hour; ARNP, advanced registered nurse practioner.

http://dx.doi.org/10.21037/jtd-21-552