Ketorolac use and anastomotic leak in patients with esophageal cancer

Erin M. Corsini, MD,[a] and Wayne L. Hofstetter, MD,[a] the MD Anderson Esophageal Cancer Working Group[a,b]

THOR

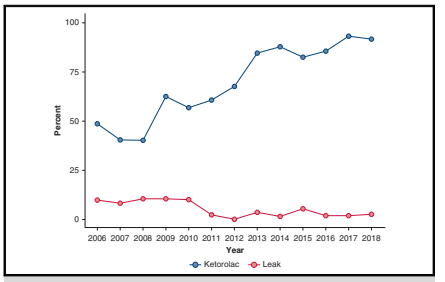
ABSTRACT

Objectives: Recent evidence has shown an association between postoperative ketorolac use and anastomotic leak in patients undergoing intestinal and colorectal operations, but this relationship has been minimally explored after esophagectomy. As the use of nonopioid pain control and enhanced recovery protocols is increasingly prioritized, determination of a possible correlation between perioperative ketorolac use and leak is essential.

Methods: Records of patients undergoing esophagectomy for adenocarcinoma at a single institution from 2006 to 2018 reviewed for occurrence of anastomotic leak. Institutional pharmacy records were queried for ketorolac administration during the surgical case through the time of discharge. Multivariable logistic regression was used to determine the relationship between ketorolac administration and anastomotic leak.

Results: A total of 1019 patients met inclusion criteria, the majority of whom were male (907, 89%) with a median age of 62 years. Patients predominantly presented with locoregionally advanced disease and were treated with initial chemoradiation. Ketorolac was administered to 686 patients (67%); use was observed to increase over the study period from 49% in 2006 to 92% in 2016. Conversely, anastomotic leak occurred in 87 patients (9%) overall and decreased over time from 15% (11/72) in 2006 to 2% (2/83) in 2018. Upon multivariable analysis, neither ketorolac administration evaluated as a categoric variable (odds ratio, 0.99; $P = .958$) or as a continuous variable using dose (odds ratio, 1.00; $P = .843$) demonstrated an association with anastomotic leak.

Conclusions: Ketorolac in the postoperative period after esophagectomy has become an integral component of enhanced recovery pathways and does not appear to be associated with anastomotic leak. (J Thorac Cardiovasc Surg 2021;161:448-54)



Percent of patients with anastomotic leak (*red*) and receiving ketorolac (*blue*) by year.

CENTRAL MESSAGE

In the setting of increasing use of ERAS pathways, ketorolac in the postoperative period does not seem to be associated with anastomotic leak after esophagectomy.

PERSPECTIVE

Consequent to ERAS pathway integration and the growing opioid epidemic, nonopioid postoperative pain management has been emphasized. Yet, concerns have been raised as to an association of NSAIDs with anastomotic leak. Our study of more than 1000 patients failed to demonstrate an association of NSAID use and anastomotic leak in patients with esophageal cancer.

See Commentaries on pages 455 and 456.

Enhanced recovery after surgery (ERAS) protocols have been widely integrated into routine postoperative practices across a variety of surgical fields. This change has been motivated by several issues, including perioperative optimization with nutritional supplementation, tobacco cessation, and physical conditioning, as well as such factors as adequate pain control, expedient recovery with return to baseline mobility, faster bowel recovery, and an opioid epidemic that is prevalent across the United States.[1,2] Postoperative analgesic medications have shifted away from single-agent opioid medications, particularly by intravenous methods, and have been replaced by multimodal analgesic approaches that include nonsteroidal anti-inflammatory drugs (NSAIDs).[3,4]

From the Departments of [a]Thoracic and Cardiovascular Surgery and [b]Anesthesiology and Perioperative Medicine, University of Texas MD Anderson Cancer Center, Houston, Tex.

Institutional Review Board Approval: The University of Texas MD Anderson Cancer Center IRB, Protocol #PA18-0774, activated December 18, 2018.

MD Anderson Esophageal Cancer Working Group: Kyle G. Mitchell, MD, Nicolas Zhou, DO, Mara B. Antonoff, MD, Reza J. Mehran, MD, Gabriel E. Mena, MD, David C. Rice, MD, Jack A. Roth, MD, Boris Sepesi, MD, Stephen G. Swisher, MD, Ara A. Vaporciyan, MD, and Garrett L. Walsh, MD.

Read at the AATS International Thoracic Surgical Oncology Summit, New York City, NY, September 27-28, 2019.

Received for publication Sept 15, 2019; revisions received Jan 30, 2020; accepted for publication Feb 4, 2020; available ahead of print March 21, 2020.

Address for reprints: Wayne L. Hofstetter, MD, Department of Thoracic and Cardiovascular Surgery, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030 (E-mail: WHofstetter@MDAnderson.org).

0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2020.02.133

Abbreviations and Acronyms

BMI = body mass index
CI = confidence interval
ERAS = enhanced recovery after surgery
IQR = interquartile range
NSAID = nonsteroidal anti-inflammatory drug
OR = odds ratio

Scanning this QR code will take you to the article title page to access supplementary information.

However, with the increasing use of NSAIDs, including ketorolac, these practices have come under particular scrutiny due to some evidence reporting associated higher rates of surgical complications, namely anastomotic leak. This relationship has been primarily explored in the setting of colorectal resections and to a lesser extent bariatric surgeries.[5-7] To date, only 1 investigation has evaluated this association in patients undergoing esophageal anastomoses and reported concerning results.[8] Because of the highly morbid nature of anastomotic leak in a population who may otherwise be deconditioned and unable to sustain such an insult, additional investigations are needed to determine if there is need for caution when using ketorolac during or after esophagectomy.[9,10] Therefore, we sought to determine whether patients with esophageal cancer receiving ketorolac as a component of ERAS pathways at our center were at increased risk for anastomotic leakage in the immediate postoperative period.

PATIENTS AND METHODS

Patient Population

Patients undergoing esophagectomy for a diagnosis of esophageal adenocarcinoma from January 1, 2006, to December 31, 2018, were retrospectively identified using a prospectively maintained thoracic surgery departmental database at the University of Texas MD Anderson Cancer Center. This retrospective study was undertaken after approval by the University of Texas MD Anderson Cancer Center Institutional Review Board with a waiver of informed consent (Protocol PA18-0774).

Various demographic, treatment, and clinicopathologic factors were evaluated as potential factors associated with anastomotic leak based on available literature and clinical experience. In addition to ketorolac use, the following demographic and clinical variables were also included: age, sex, smoking history, body mass index (BMI), Zubrod performance status, clinical T-status, clinical N-status, type of esophagectomy, salvage esophagectomy, use of ERAS protocols, operative estimated blood loss, operative duration, cancer treatment strategy (upfront esophagectomy vs initial chemoradiation), and pretreatment tumor size based on endoscopic assessment. At our institution, the integration of ERAS protocols into routine practice began in January 2012; as such, pre-ERAS was defined by surgical resection occurring before this date, and this was evaluated as an independent factor associated with leak.[11] Briefly, our ERAS protocol allows for a clear liquid diet up to 2 hours before surgery, preoperative analgesia, multimodal opioid-sparing postoperative analgesia, and early ambulation, among other factors. Because the study period spanned several iterations of cancer staging systems, clinical staging was defined by the 6th edition of the American Joint Committee on Cancer. Patients undergoing right transthoracic (Ivor Lewis), transhiatal, 3-hole, and minimally invasive Ivor Lewis esophagectomy (including robotic) were included in the analysis; minimally invasive procedures included hybrid approaches. In terms of oncologic treatment paradigm, only patients who received upfront esophagectomy or neoadjuvant chemoradiation followed by esophagectomy were included in the study; those who received only chemotherapy or radiotherapy alone followed by resection were excluded. Postoperative dietary management was at the discretion of the attending surgeon.

Ketorolac Administration

Institutional pharmacy records were queried for ketorolac use intraoperatively through the time of discharge. Discharge medications were not included in the analysis. Further, ketorolac use was first assessed in a binary manner, such that patients were categorized as having received or not received ketorolac. Additional pharmacy records were then evaluated to include a dose variable, which was calculated as the sum total dose of ketorolac received, in milligrams, over the length of postoperative hospitalization. Patients who had not received ketorolac at all were said to have received a dose of 0 mg for this period.

Determination of Anastomotic Leak

During the study period, practices within our department shifted from routine postoperative screening for anastomotic leak in all patients with appropriate imaging to selective evaluation if clinically indicated or leak was suspected. If a leak was suspected clinically, appropriate axial imaging, endoscopic evaluation, or swallow study was undertaken at the discretion of the attending surgeon. Detection of a leak was classified by grade, in methods that have been described.[12] For purposes of this investigation, we have defined anastomotic leak as those categorized as type II or greater, that is, necessitating endoscopic, percutaneous, or surgical intervention.

Statistical Methods

Categoric variables were analyzed using Pearson's chi-square or Fisher exact tests where appropriate, and continuous variables were analyzed using the Mann–Whitney *U* and Kruskal–Wallis tests. All analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria; http://r-project.org) and RStudio software Version 1.1.463 (RStudio, Inc, Boston, Mass).

Univariable logistic regression was conducted to determine evaluate covariates to be included in a model for anastomotic leak. Surgical year was tested as a possible covariate to account for temporal changes over the study period. As the variable of interest, ketorolac administration was selected a priori for inclusion in the multivariable model. Then, backwards stepwise elimination was performed via sequential evaluation of the Akaike information criterion. The final multivariable logistic regression model was used to determine if ketorolac use was associated with anastomotic leak in patients undergoing esophagectomy for a diagnosis of esophageal adenocarcinoma.

RESULTS

There were 1016 patients who met inclusion criteria, the majority (907, 89%) of whom were male with a median age of 62 years (interquartile range [IQR], 55-69) (Table 1). Most patients were overweight (median BMI 28.3 kg/m^2; IQR, 25.1-31.5) and ever-smokers (674, 66%). Diabetes mellitus and coronary artery disease were the most frequent

TABLE 1. Patient, operative, and tumor characteristics (n = 1016)

Variable	n (%) or Median (IQR)		*P* value
	Pre-ERAS (n = 524)	ERAS (n = 492)	
Male sex	471 (90)	434 (88)	.451
Median age, y	62 (55-68)	63 (56-69)	.128
Median BMI, kg/m^2	28.3 (25.1-31.4)	28.5 (25.1-31.5)	.922
Zubrod performance status ≥1	213 (41)	167 (34)	.034
Ever-smoker	391 (75)	283 (58)	<.001
COPD	32 (6)	24 (5)	.471
Coronary artery disease	89 (17)	65 (13)	.112
Renal insufficiency*	3 (1)	8 (2)	.187
Diabetes mellitus	89 (17)	86 (17)	.900
Clinical T3-4 (vs Tis-2)†	354 (68)	392 (80)	<.001
Clinical N+ (vs N0)†	261 (50)	275 (56)	.084
Salvage esophagectomy	90 (17)	156 (32)	<.001
Type of esophagectomy			<.001
Right transthoracic (Ivor Lewis)	353 (67)	352 (72)	
Transhiatal	47 (9)	10 (2)	
3-hole	17 (3)	17 (3)	
Minimally invasive	107 (20)	113 (23)	
EBL, mL	450 (300-600)	350 (235-513)	<.001
Operative duration, h	6.0 (5.2-6.9)	6.0 (5.0-7.1)	.741
Chemoradiation (vs upfront esophagectomy)	423 (81)	438 (89)	<.001
Pretreatment tumor size, cm	5.0 (3.0-6.0)	4.0 (3.0-6.0)	.183
Ketorolac administration	270 (52)	416 (85)	<.001
Median ketorolac dose, mg‡	150 (90-225)	150 (120-240)	<.001
Median hospital length of stay, d	9 (7-13)	8 (7-11)	<.001
Anastomotic leak	68 (13)	19 (4)	<.001

ERAS, Enhanced recovery after surgery; *IQR,* interquartile range; *BMI,* body mass index; *COPD,* chronic obstructive pulmonary disease; *EBL,* estimated blood loss. *Defined by creatinine 2 mg/dL or greater or need for dialysis. †Defined by American Joint Committee on Cancer 6th Edition. ‡Of 686 patients who received ketorolac.

comorbid conditions (17% and 15%, respectively), whereas a history of renal insufficiency defined by creatinine 2 mg/dL or greater or need for dialysis was rare (11/1016, 1%). With respect to disease characteristics, tumors were typically transmural (cT3-4: 746/1016, 73%), and approximately one-half had clinical N-positive disease. Neoadjuvant or definitive (before salvage surgery) chemoradiation was administered to 85% of our cohort of patients. The most common approach to resection was right transthoracic (Ivor Lewis) esophagectomy (705, 69%), and 22% (220/1016) underwent minimally invasive Ivor Lewis esophagectomy. A majority of patients had an anastomosis in the chest (894, 88%); fewer patients had neck (123, 12%) or abdominal anastomoses (2, 0.1%). A gastric conduit was used for most patients (992, 97%), and use of free flap jejunal interposition (12, 1%), pedicled jejunum (14, 1%), or colon (1, 0.1%) was uncommon. Median hospital length of stay was 9 days (IQR, 7-13). Median operative duration and blood loss were 5.7 hours and 400 mL, respectively. By using the date of incorporation of ERAS protocols, 48% of patients underwent surgery using ERAS. Patients undergoing surgery in the ERAS period more likely to be never-smokers undergoing Ivor Lewis or salvage esophagectomy, and were more likely to have received ketorolac.

With respect to ketorolac use, 686 patients (67%) received this medication during their index hospitalization. Of those who received ketorolac, the median sum total dose received over the hospitalization period was 150 mg (IQR, 120-240). The use of ketorolac increased steadily over the study period, with 49% (35/72) of patients undergoing esophagectomy in 2006 receiving ketorolac during their hospitalization, whereas nearly all patients (76/83, 92%) in the final year received this medication (Figure 1). Conversely, the incidence of anastomotic leak decreased over the course of the study timeframe. Overall, 55 patients

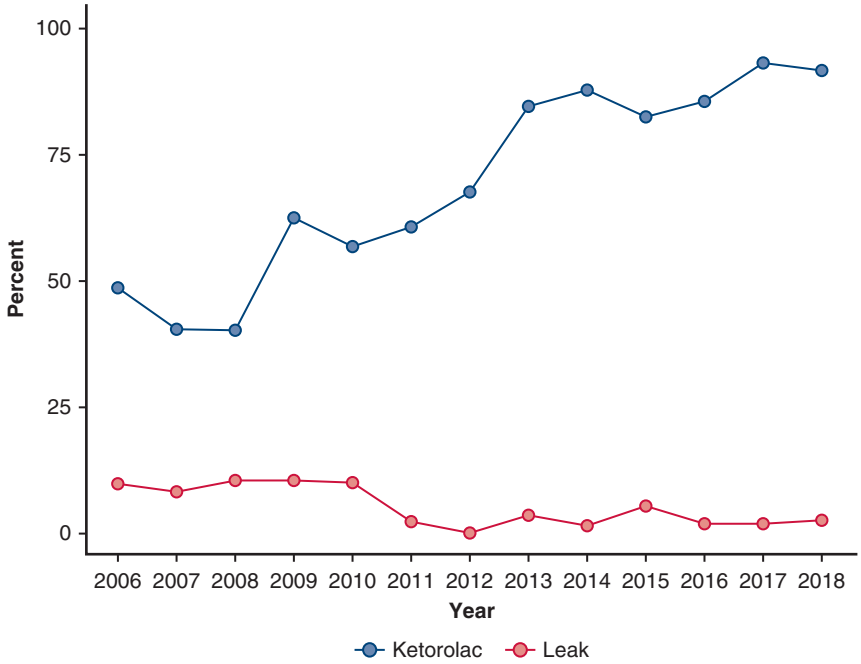


FIGURE 1. Percentage of patients with anastomotic leak (*red*) and receiving perioperative ketorolac (*blue*) after esophagectomy by year.

(5%) had leak. In 2006, leak occurred in 7 of 72 patients (10%), whereas this decreased to only 2% (2/83) of cases in the final study year.

Upon comparing those patients with and without anastomotic leak, patients did not differ in terms of sex ($P = 1.000$), smoking history ($P = .239$), or comorbid conditions (Table 2). A greater proportion of patients undergoing esophagectomy via a transhiatal or minimally invasive Ivor Lewis approach had anastomotic leak when compared with those undergoing esophagectomy via alternate approaches ($P = .022$). Ketorolac was administered less commonly among patients who had leak than in those who did not ($P = .049$). Occurrence of leak in patients receiving 0 mg, 1 to 150 mg, and greater than 150 mg of ketorolac during their hospitalization was 8% (25/330), 5% (14/281), and 4% (16/405) ($P = .090$).

Next, several factors were tested to determine the relationship with anastomotic leak with various clinical and demographic variables. Upon univariable logistic regression, Zubrod performance status, type of esophagectomy, ERAS pathway use, clinical T stage, and ketorolac use were found to be associated with the outcome, and thus were included in a final multivariable model (Table 3); history of diabetes mellitus or chronic obstructive pulmonary disease and tumor location were not associated with leak. Multivariable analysis revealed that ERAS protocols (odds ratio [OR], 0.27; 95% confidence interval [CI], 0.13-0.56; $P < .001$) were associated with the outcome of anastomotic leak. Specifically, ketorolac use was not determined to be related to the occurrence of postoperative anastomotic leak (OR, 0.89; 95% CI, 0.49-1.59; $P = .688$). Upon evaluation for multicollinearity between ERAS pathway use and ketorolac use, the 2 variables were not found to be highly correlated (ERAS variance inflation factor: 1.011, ketorolac variance inflation factor: 1.10).

We evaluated ketorolac dose in milligrams among all patients as a continuous variable, with a dose of 0 mg assigned to patients who did not receive any ketorolac. In this model, we again were unable to demonstrate a relationship between ketorolac dosage and occurrence of anastomotic leak (OR, 1.00; 95% CI, 1.00-1.00; $P = .527$).

To attempt to account for practices differences among attending surgeons, as well as practices shifts over this prolonged study period, both surgeon and surgery were evaluated as covariates. However, surgeon and year were not associated with the outcome of anastomotic leak.

Subgroup Analysis

In an effort to minimize those unmeasured variables that may otherwise have contributed to outcomes, such as operative volume and technique, a subset analysis was conducted in which only those patients undergoing open Ivor Lewis esophagectomy with the single highest-volume surgeon were assessed (n = 244). Leak occurred in 16 (7%), and a majority of patients received ketorolac (n = 169, 69%). ERAS use (OR, 0.26; 95% CI, 0.051-0.73; $P = .023$) and ketorolac (OR, 0.32; 95% CI, 0.11-0.88; $P = .029$) were included in a multivariate model, whereupon neither was associated with the outcome of leak (ERAS: OR, 0.28, $P = .061$; ketorolac: OR, 0.43, $P = .117$) (Table 4).

TABLE 2. Characteristics by anastomotic leak status

Variable	n (%) or median (IQR)		*P* value
	No leak (n = 961)	Leak (n = 55)	
Male sex	856 (89)	49 (89)	1.000
Median age, y	62 (55-69)	64 (58-69)	.447
Median BMI, kg/m^2	28.3 (25.1-31.5)	28.9 (26.0-31.2)	.583
Zubrod performance status ≥1	352 (37)	28 (51)	.049
Ever-smoker	633 (66)	41 (75)	.239
COPD	53 (6)	3 (5)	1.00
Coronary artery disease	144 (15)	10 (18)	.653
Renal insufficiency*	11 (1)	0 (0)	1.00
Diabetes mellitus	165 (17)	10 (18)	.992
Salvage esophagectomy	233 (24)	13 (24)	.012
Type of esophagectomy			.022
Right transthoracic (Ivor Lewis)	674 (70)	31 (56)	
Transhiatal	51 (5)	6 (11)	
3-hole	34 (4)	0 (0)	
Minimally invasive	202 (21)	18 (33)	
Ketorolac administration	656 (68)	30 (55)	.049
Total ketorolac dose, mg			.090
0	305 (32)	25 (45)	
1-150	267 (28)	14 (25)	
>150	389 (40)	16 (29)	

IQR, Interquartile range; *BMI,* body mass index; *COPD,* chronic obstructive pulmonary disease. *Defined by creatinine 2 mg/dL or greater or need for dialysis.

DISCUSSION

In the present study, we aimed to determine whether a relationship exists between ketorolac use in patients undergoing esophagectomy for esophageal adenocarcinoma at our center and the occurrence of anastomotic leak. To this end, we queried institutional pharmacy records to first determine the subset of patients who received this medication and to assess the potential for a dose-response relationship. We found that despite marked increases in ketorolac use during our study period, use was not associated with anastomotic breakdown (Video 1). Additionally, higher total doses of ketorolac over the postoperative hospitalization do not appear to increase the risk for leak.

In an age of prevalent ERAS pathways and concerns regarding opioid overuse, our report adds timely and reassuring data to the conversation of best treatment practices for esophagectomy cases postoperatively. Anastomotic leak poses significant risk of death to those undergoing esophagectomy, and so there is appropriate cause for concern.[9] As discussed, owing largely to its incorporation into ERAS protocol as a mainstay of pain control, ketorolac use at our institution more than doubled over the course of our study period.[13] Furthermore, whether the baseline characteristics and perioperative management strategies of the examined cohort are reflective of an American surgical population cannot be gleaned.

To the authors' knowledge, only one study exists to date that previously evaluated the relationship between esophageal anastomotic leak and NSAID use.[8] In this Danish trial of 557 patients, ketorolac use in the first 7 postoperative days was demonstrated to be associated with leak; however, the proportion of patients receiving this medication was relatively small, which may have introduced considerable variability, although similar leak rates were observed.

The literature in the realm of colorectal cancer has similarly reported mixed findings. When several NSAIDs, including ketorolac, were evaluated, medication use was not deemed to be a risk factor for leak.[14,15] Conversely, among a large national database with relatively sparse ketorolac use, it was nonetheless found to be associated with complications; however, in this study, procedure codes were used to define a complication, and so extrapolation of the precise event is unclear.[16] In attempts to assess the available literature, several systematic reviews and meta-analyses, have offered reassuring data, namely, that NSAIDs do not pose increased risk of leak.[5,6] Additionally, in an retrospective case-control study of NSAID use after bariatric surgery, no differences were observed in leak rates between groups.[7]

The relationship between NSAIDs and wound healing remains largely theoretical, although animal models exist to demonstrate possible mechanisms. It is thought that, similar

TABLE 3. Univariable and multivariable logistic regression analyses for anastomotic leak

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, y	1.01 (0.99-1.04)	.379		
Female sex	1.00 (0.38-2.21)	.997		
BMI, kg/m^2	1.01 (0.96-1.05)	.696		
Zubrod performance status ≥1	1.79 (1.03-3.09)	.037	1.68 (0.96-2.93)	.069
Ever-smoker	1.52 (0.84-2.92)	.188		
Diabetes mellitus	1.07 (0.50-2.09)	.847		
COPD	0.99 (0.24-2.80)	.985		
ASA class>2	0.90 (0.38-2.63)	.820		
Clinical T3-4 (vs Tis-2)	0.61 (0.35-1.09)	.089		
Clinical N+ (vs N0)	1.06 (0.61-1.84)	.840		
Upfront esophagectomy (vs trimodality therapy)	1.42 (0.68-2.72)	.317		
Salvage esophagectomy	0.97 (0.49-1.78)	.915		
Type of esophagectomy				
Ivor Lewis	Ref		Ref	
Transhiatal	2.56 (1.02-6.41)	.045	1.71 (0.67-4.38)	.260
Three-hole	0 (0-NR)	.983	0 (0-NR)	.982
Minimally invasive	1.94 (1.06-3.54)	.031	2.05 (1.11-3.78)	.022
ERAS use	0.25 (0.12-0.47)	<.001	0.27 (0.13-0.56)	<.001
EBL, L	1.09 (0.47-2.01)	.824		
Operative duration, min	1.00 (1.00-1.00)	.371		
Ketorolac use	0.56 (0.32-0.97)	.037	0.89 (0.49-1.59)	.688
Pretreatment tumor size, cm	1.07 (0.97-1.16)	.154		

OR, Odds ratio; *CI,* confidence interval; *BMI,* body mass index; *COPD,* chronic obstructive pulmonary disease; *ASA,* American Society of Anesthesiologists; *NR,* not reached; *ERAS,* enhanced recovery after surgery; *EBL,* estimated blood loss.

to steroids, the anti-inflammatory properties of ketorolac and other NSAIDs decrease recruitment and migration of several inflammatory cells that would otherwise promote efficient wound healing at maximal tensile strength.[17]

We present our large, single-center experience evaluating routine NSAID integration into the care of esophagectomy cases. Using well-documented pharmacy records, we have been able to comprehensively evaluate the medication use of the patients in our cohort during their postoperative hospitalization, including the detailed dosages over this time. We believe that our incidence of leak is consistent with the literature and that the perioperative management strategies represented in the work are consistent with the practices of academic thoracic surgeons.[9,18-20]

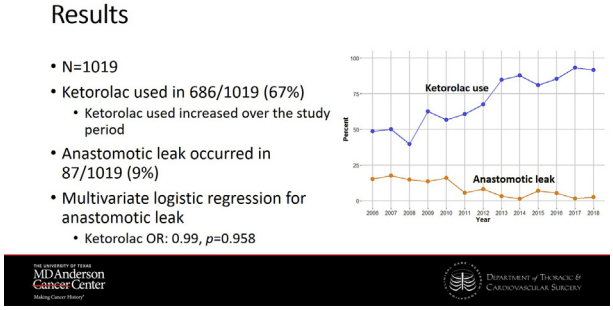
TABLE 4. Subset analysis for anastomotic leak (n = 244)

Variable	OR (95% CI)	*P* value
ERAS use	0.28 (0.06-0.95)	.061
Ketorolac use	0.43 (0.14-1.24)	.117

Additional factors tested in univariable analysis included: age, gender, diabetes mellitus, chronic obstructive pulmonary disease, BMI, smoking status, clinical stage, operative blood loss and duration, preoperative treatment, tumor size. *OR,* Odds ratio; *CI,* confidence interval; *ERAS,* enhanced recovery after surgery.

Study Limitations

We acknowledge that there are limitations to our report, including its retrospective design. Although we have attempted to account for various patient and disease factors in our regression model, there may yet be unmeasured confounders such as practice differences among surgeons, including anastomotic technique, use of an omental flap,



VIDEO 1. Ketorolac use in enhanced recovery protocols is not associated with anastomotic leak among patients undergoing esophagectomy. Video available at: https://www.jtcvs.org/article/S0022-5223(20)30632-2/fulltext.

and various gastric drainage procedures. Additional temporal changes over the study duration may be unmeasured, including shifts from mandated to selective assessment for leak, improved proficiency with minimally invasive techniques, changes to multimodality treatment algorithms, and increasing use of omental reinforcement flaps.[12] Our work represents the experience of a single, large, tertiary referral care center; thus, the extent to which our results are generalizable to the overall population is uncertain. Generalizability may be limited by differing imaging surveillance and management practices, particularly for nonclinically significant leaks, as we have defined in our study; the relationship between ketorolac and such leaks remains unknown. Because we defined medication use by the postoperative hospitalization, we are unable to assess the use of preoperative NSAID use, and the extent to which this may have influenced outcomes. Although we acknowledge these limitations, we would submit that our findings offer reassurance in a topical field with a paucity of data.

CONCLUSIONS

As a keystone component of multimodal pain control regimens, ketorolac does not appear to increase the risk of anastomotic leak in an otherwise potentially deconditioned population of patients with esophageal cancer. In the absence of contraindications and prospective studies, the potential risks and benefits of NSAID use as a component of ERAS protocols should be weighed and used cautiously.

Conflict of Interest Statement

Dr Hofstetter discloses personal fees from Johnson & Johnson. Corsini has nothing to disclose with regard to commercial support.

The authors thank Chun Feng and the University of Texas MD Anderson Cancer Center Institutional Analytics and Informatics Support Team, who were instrumental in identifying the individuals for inclusion in our study cohort.

References

1. Beverly A, Kaye AD, Ljungqvist O, Urman RD. Essential Elements of Multimodal Analgesia in Enhanced Recovery After Surgery (ERAS) Guidelines. *Anesthesiol Clin*. 2017;35:e115-43.
2. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: a review. *JAMA Surg*. 2017;152:292-8.
3. Chapman SJ, Garner JJ, Drake TM, Aldaffaa M, Jayne DG. Systematic review and meta-analysis of nonsteroidal anti-inflammatory drugs to improve GI recovery after colorectal surgery. *Dis Colon Rectum*. 2019;62:248-56.
4. Nimmo SM, Foo ITH, Paterson HM. Enhanced recovery after surgery: pain management. *J Surg Oncol*. 2017;116:583-91.
5. Huang Y, Tang SR, Young CJ. Nonsteroidal anti-inflammatory drugs and anastomotic dehiscence after colorectal surgery: a meta-analysis. *ANZ J Surg*. 2018;88:959-65.
6. Modasi A, Pace D, Godwin M, Smith C, Curtis B. NSAID administration post colorectal surgery increases anastomotic leak rate: systematic review/meta-analysis. *Surg Endosc*. 2019;33:879-85.
7. Abou Zeid H, Kallab R, Najm MA, Jabbour H, Noun R, Sleilati F, et al. Safety and efficacy of non-steroidal anti-inflammatory drugs (NSAIDs) used for analgesia after bariatric surgery: a retrospective case-control study. *Obes Surg*. 2019;29:911-6.
8. Fjederholt KT, Okholm C, Svendsen LB, Achiam MP, Kirkegard J, Mortensen FV. Ketorolac and other NSAIDs increase the risk of anastomotic leakage after surgery for GEJ cancers: a cohort study of 557 patients. *J Gastrointest Surg*. 2018;22:587-94.
9. Jones CE, Watson TJ. Anastomotic leakage following esophagectomy. *Thorac Surg Clin*. 2015;25:449-59.
10. Dasari BV, Neely D, Kennedy A, Spence G, Rice P, Mackle E, et al. The role of esophageal stents in the management of esophageal anastomotic leaks and benign esophageal perforations. *Ann Surg*. 2014;259:852-60.
11. Van Haren RM, Mehran RJ, Mena GE, Correa AM, Antonoff MB, Baker CM, et al. Enhanced recovery decreases pulmonary and cardiac complications after thoracotomy for lung cancer. *Ann Thorac Surg*. 2018;106:272-9.
12. Sepesi B, Swisher SG, Walsh GL, Correa A, Mehran RJ, Rice D, et al. Omental reinforcement of the thoracic esophagogastric anastomosis: an analysis of leak and reintervention rates in patients undergoing planned and salvage esophagectomy. *J Thorac Cardiovasc Surg*. 2012;144:1146-50.
13. Wick EC, Grant MC, Wu CL. Postoperative multimodal analgesia pain management with nonopioid analgesics and techniques: a review. *JAMA Surg*. 2017;152:691-7.
14. Rushfeldt CF, Agledahl UC, Sveinbjornsson B, Soreide K, Wilsgaard T. Effect of perioperative dexamethasone and different NSAIDS on anastomotic leak risk: a propensity score analysis. *World J Surg*. 2016;40:2782-9.
15. Saleh F, Jackson TD, Ambrosini L, Gnanasegaram JJ, Kwong J, Quereshy F, et al. Perioperative nonselective non-steroidal anti-inflammatory drugs are not associated with anastomotic leakage after colorectal surgery. *J Gastrointest Surg*. 2014;18:1398-404.
16. Kotagal M, Hakkarainen TW, Simianu VV, Beck SJ, Alfonso-Cristancho R, Flum DR. Ketorolac use and postoperative complications in gastrointestinal surgery. *Ann Surg*. 2016;263:71-5.
17. Fairweather M, Heit YI, Buie J, Rosenberg LM, Briggs A, Orgill DP, et al. Celecoxib inhibits early cutaneous wound healing. *J Surg Res*. 2015;194:717-24.
18. Dent B, Griffin SM, Jones R, Wahed S, Immanuel A, Hayes N. Management and outcomes of anastomotic leaks after oesophagectomy. *Br J Surg*. 2016;103:1033-8.
19. Semenkovich TR, Hudson JL, Subramanian M, Kozower BD. Enhanced Recovery After Surgery (ERAS) in thoracic surgery. *Semin Thorac Cardiovasc Surg*. 2018;30:342-9.
20. Gonfiotti A, Viggiano D, Bongiolatti S, Bertolaccini L, Solli P, Bertani A, et al. Enhanced Recovery After Surgery (ERAS((R))) in thoracic surgical oncology. *Future Oncol*. 2018;14:33-40.

Key Words: anastomotic leak, esophageal cancer, esophagectomy, ketorolac, NSAIDs