Serial Drain Amylase Can Accurately Detect Anastomotic Leak After Esophagectomy and May Facilitate Early Discharge

Yaron Perry, MD, Christopher W. Towe, MD, Jonathan Kwong, MD, Vanessa P. Ho, MD, and Philip A. Linden, MD

Division of Thoracic and Esophageal Surgery, University Hospitals Case Medical Center and Case Western Reserve School of Medicine, Cleveland, Ohio

Background. **Anastomotic leaks after esophagectomy are a significant cause of postoperative morbidity and death. Barium esophagram and esophagogastroduodenoscopy are commonly used to survey for leaks; however, each has inherent risks and limitations. We sought to evaluate the effectiveness of daily drain amylase levels in detecting anastomotic leaks after esophagectomy.**

Methods. **We retrospectively reviewed 146 consecutive patients who underwent esophagectomy with cervical and intrathoracic anastomosis using gastric conduit. We collected daily drain amylase levels and obtained postoperative barium esophagrams routinely. Receiver operating characteristic analysis was performed to evaluate the ability of drain amylase to detect anastomotic leaks and to determine the sensitivity and specificity at various cutoff values.**

Results. **There were no in-hospital or outpatient deaths within 30 days of operation in this consecutive series of patients. A leak occurred in 22 of 146 esophagectomy patients (15%) that required postoperative intervention. An additional 13 patients (9%) had a leak requiring only alteration of diet or antibiotics. The sensitivity and specificity for barium esophagram was 36.9% and 95%, respectively. For drain amylase obtained on postoperative day 4, a cutoff of 38 IU/L yielded a sensitivity of 100% and a specificity of 52.0%, and a cutoff of 250 IU/L yielded a sensitivity of 66.7% and a specificity of 95.9% in detecting leaks eventually requiring intervention.**

Conclusions. **Drain amylase levels recorded on day 4 after esophagectomy are more accurate for the detection of esophageal anastomotic leak than barium esophagram. Drain amylase levels represent a noninvasive test that may facilitate safe, early discharge after esophagectomy.**

(Ann Thorac Surg 2015;■:■–■)

The mortality rate associated with esophageal resection has decreased over time and is now approximately 3% at experienced centers. The morbidity of the operation remains significant, however, at 40% to 50% [1]. One of the most morbid complications is anastomotic leak, with improperly treated leaks resulting in sepsis, fistula, conduit loss, or death.

The diagnosis and timely treatment of anastomotic leak is a priority of perioperative care. In fact, discharge after esophagectomy may be delayed due to concern for delayed presentation of esophageal leak. Esophageal leak can be difficult to diagnose and may present with clinical signs and symptoms ranging from tachycardia, tachypnea, pain, wound cellulitis or drainage, and hypotension. Barium esophagram has been the standard for diagnosing esophageal leaks, but its accuracy is limited in clinical practice, and may miss a significant number of leaks if performed before 7 days after cervical anastomosis [2].

Our practice has been to leave a perianastomotic drain routinely and check drain amylase levels daily. We have used drain amylase data, along with other clinical findings and barium swallow, to manage our patients. We sought to analyze drain amylase levels to determine the accuracy of these levels to detect or predict leak, or both, and how best to use these levels in managing post-esophagectomy patients.

Patients and Methods

The University Hospitals Case Medical Center Institutional Review Board approved this study. Consecutive patients undergoing esophagectomy between March 2007 and June 2014 by the Division of Thoracic and Esophageal Surgery at the University Hospital Case Medical Center were identified in our prospectively collected, Society of Thoracic Surgeons database. All adult patients undergoing esophagectomy with gastric conduit replacement were included. The hospital record of each patient was

Accepted for publication May 15, 2015.

Presented at the Fifty-first Annual Meeting of The Society of Thoracic Surgeons, San Diego, CA, Jan 24–28, 2015.

Address correspondence to Dr Perry, University Hospitals Case Medical Center, Division of Thoracic and Esophageal Surgery, 11100 Euclid Ave, Cleveland, OH 44106-5011; e-mail: yaron.perry@uhhospitals.org.

Published by Elsevier

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2015.05.092

reviewed to define the surgical procedure, anastomotic technique (stapled, handsewn, or hybrid), esophagram date and results, and daily drain amylase levels. Esophagectomies were classified as tri-incisional, Ivor Lewis, or transhiatal. An operation was termed minimally invasive if the chest or abdominal portion of the operation was performed entirely using thoracoscopic or laparoscopic techniques.

Tumor characteristics, comorbidities, transfusions, and complications were extracted from The Society of Thoracic Surgeons database. Additional outcomes of interest collected included the hospital length of stay and combined in-hospital and 30-day mortality.

A retrospective record review was used to determine the attending surgeon's determination of whether an esophageal leak had occurred and how and when it was treated. Anastomotic leak was defined as clinical or radiologic evidence of a full-thickness gastrointestinal defect involving the esophagus, anastomosis, staple line, or conduit. Leaks were classified into 3 grades as grade I: local defect requiring no change in therapy or treated medically or with dietary modification; grade II: localized defect requiring interventional (eg, interventional radiology drain, stent, or bedside opening and packing of incision) but not surgical therapy; and grade III: defect requiring unplanned reoperation [3].

Postoperative drain amylase levels were recorded through postoperative day 5 unless a clinical leak was diagnosed earlier. In the event that more than one amylase level was assessed on the same day, the highest amylase level was used in the analysis. Amylase levels obtained after an intervention for leak were excluded. Esophagram date and results were recorded, and esophagrams performed after an intervention for leak were excluded.

Data are presented as mean and standard deviation. Two-group comparisons were performed using the Student t test or χ^2 analysis, as appropriate ($\alpha < 0.05$). The area under curve the receiver operating characteristic (ROC) curve was determined for amylase level and leak. Sensitivity and specificity were calculated at varying amylase levels and on different postoperative days to determine the day and value at which amylase identified the leak with the highest accuracy, sensitivity, and specificity. These data were compared with our own esophagram results and with historical series in the medical literature. Data were analyzed using STATA/IC 11.0 software (StataCorp LP, College Station, TX).

Results

A retrospective review identified 146 patients who met the inclusion criteria and were included in the analysis. Patient characteristics are summarized in Table 1. Approximately 60% of our patients received neoadjuvant chemoradiotherapy. The procedures performed and anastomotic types are summarized in Table 2. The anastomosis was cervical in 82% of patients and intrathoracic in 18%. More than half of the esophagectomies were done minimally invasively. Nearly all of the anastomoses were performed with some type of stapled technique.

Table 1. Patient Characteristics

Variable	No.	Median (range) or No. (%)
Age, y		64.6 (25.5–84.8)
Male sex	146	114 (78.1)
Race	146	
White		136 (93.2)
Black		10 (6.8)
Body mass index, kg/m^2	77	28.1 (16.3–53.8)
Hypertension	144	85 (59.0)
Coronary artery disease	144	30 (20.8)
Diabetes	146	29 (19.9)
COPD	119	11 (9.2)
Preoperative chemotherapy	120	72 (59.1)
Preoperative radiotherapy	144	83 (57.6)

COPD = chronic obstructive pulmonary disease.

Figure 1 summarizes the leak rate by grade. Some degree of leak was identified in 35 patients (24%); of these, 13 (8.9%) were treated medically (grade I), and 22 (15.1%) were deemed to have a clinically significant leak requiring more than just dietary modification or antibiotics (grade II or III). The leak rate according to the type of operation performed is described in Table 3. The leak rate was not statistically different between procedures performed ($p = 0.28$) or anastomotic technique ($p = 0.26$).

Drain amylase levels were higher in patients with esophageal leak (grade I, II, or III) on postoperative days 2, 4, and 5 (Table 4). These differences were more pronounced among patients who had clinically significant leaks (grade II or III), and were statistically significant on postoperative days 1, 2, 3, 4, and 5 (Table 5).

Drain amylase levels from postoperative days 3, 4, and 5 were used to construct ROC curves. The areas under the curve for drain amylase collected on postoperative days 3, 4, and 5 in detecting all esophageal leaks were 0.68, 0.79,

Table 2. The Procedure Performed and Type of Anastomosis

Procedure/Anastomosis Performed	No. (%) (n = 146)
Transhiatal	36 (24.6)
Ivor Lewis	
Open	5 (3.4)
Minimally invasive	20 (13.7)
3 Hole	
Open	20 (13.7)
Minimally invasive	64 (43.8)
Thoracoabdominal	1 (0.7)
Linear stapled	66 (45.2)
Hybrid[a]	52 (35.6)
Circular stapled	27 (18.5)
Handsewn	1 (0.7)

[a] Partially linear stapled and partially handsewn.