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ORIGINAL ARTICLE

Gastric Ischemic Conditioning Prior to Esophagectomy Is Associated with Decreased Stricture Rate and Overall Anastomotic Complications

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Abstract

Background Gastric ischemic conditioning prior to esophagectomy can increase neovascularization of the new conduit. Prior studies of ischemic conditioning have only investigated reductions in anastomotic leaks. Our aim was to analyze the association between gastric conditioning and all anastomotic outcomes as well as overall morbidity in our cohort of esophagectomy patients.

Methods We performed a retrospective review of patients undergoing esophagectomy from 2010 to 2015 in a National Cancer Institute designated center. Ischemic conditioning (IC) was performed on morbidly obese patients, those with cardiovascular disease or uncontrolled diabetes, and those requiring feeding jejunostomy and active tobacco users. IC consisted of transection of the short gastric vessels and ligation of the left gastric vessels. Primary outcomes consisted of all postoperative anastomotic complications. Secondary outcomes were overall morbidity.

Results Two-hundred and seven esophagectomies were performed with an average follow-up of 19 months. Thirty-eight patients (18.4%) underwent conditioning (IC). This group was similar to patients not conditioned (NIC) in age, preoperative pathology, and surgical approach. Five patients in the ischemic conditioning group (13.2%) and 57 patients (33.7%) in the NIC experienced anastomotic complications ($p = 0.011$). Ischemic conditioning significantly reduced the postoperative stricture rate fourfold (5.3 vs. 20.7% $p = 0.02$). IC patients experienced significantly fewer complications overall (36.8 vs. 56.2% $p = 0.03$).

Conclusions Gastric ischemic conditioning is associated with fewer overall anastomotic complications, fewer strictures, and less morbidity. Randomized studies may determine optimal selection criteria to determine whom best benefits from ischemic conditioning.

Keywords Ischemic conditioning · Esophagectomy · Anastomotic complication · Esophageal cancer

Introduction

The incidence of esophageal cancer is increasing worldwide, with nearly half a million incident cases in 2008 alone.[1] In the USA, adenocarcinoma of the esophagus has an estimated overall 5-year survival no better than 15%.[2] While surgical outcomes for esophageal resection have steadily improved over time with the advent of minimally invasive techniques and improved perioperative care, surgeons continually strive to investigate etiologies of morbidity that can be altered to improve postoperative outcomes.[2–6] Though the majority of morbidity after esophagectomy is related to pulmonary complications, an associated morbidity is due to anastomotic complications.[3] The etiology of anastomotic complications is likely multifactorial, though tissue ischemia of the newly formed gastric conduit is a key factor in the development of these feared complications.

Ischemic conditioning (IC) of the stomach was first described almost 20 years ago and has shown improvement in blood flow to the future site of anastomosis by hypertrophy and neovascularization from the remaining arterial supply.[7–9] Though some published reports have shown reduction in the incidence and severity of anastomotic leaks after ischemic conditioning, these results

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have not been reliably reproduced.[10–12] Moreover, the majority of IC studies were designed to analyze improvement in anastomotic leak outcomes and neglect other important anastomotic complications.

The purpose of our study is to determine if gastric ischemic conditioning is associated with a reduction of anastomotic complications and overall post-esophagectomy morbidity. We hypothesize that ischemic conditioning would have a reduced association with overall morbidity and anastomotic complications.

Methods

Patient Selection

We performed a retrospective review of a prospectively maintained esophageal disease registry from a single National Cancer Institute designated center. Patients undergoing esophagectomy for benign or malignant disease between January 2010 and December 2015 were included in the study. Available demographic, laboratory, and staging data were collected through chart review. Preoperative medical comorbidities were tracked and recorded and an age-adjusted Charlson Comorbidity Index (CCI) was calculated.[13] All surgical procedures were performed by three institutional foregut surgeons.

Ischemic Conditioning

Under our institutional protocol, patients were selected for ischemic conditioning (IC) if they required operative feeding jejunostomy placement prior to esophagectomy due to an esophageal obstruction with inability to adequately achieve oral intake. In this group, ischemic conditioning was completed at the time of feeding tube access. Separate from the need for feeding jejunostomy, we believe that those with active tobacco use are at increased risk of anastomotic complications from microvascular disease. As such, active tobacco users were selected for IC. Patients with cardiovascular disease, severe obesity, and long-term, poorly controlled diabetes (defined by hemoglobin A1c > 8%) were also considered for IC as the authors previously showed these factors to be associated with perioperative morbidity and mortality.[14] Surgeon discretion allowed for patients to not undergo IC, if deemed clinically important.

The ischemic conditioning and feeding jejunostomy procedure were performed through a laparoscopic approach. Conditioning consisted of a partial ischemia procedure. Ultrasonic shears were used to transect the short gastric arteries. Next, the left gastric vessels were identified and a 10-mm clip was placed across them. Patients were then discharged after recovery from surgery and all patients with malignancy followed oncologic standard of care.

Statistical Analysis

The primary outcomes of this study were post-esophagectomy anastomotic complications. This included anastomotic leak, stricture, conduit ischemia, and fistula formation. The gastric conduit is half of the anastomotic complex (along with the cervical esophagus). Thus, patients who were left in discontinuity and required staged procedures for restoration of gastrointestinal continuity as a consequence of conduit ischemia were also included in this study. Anastomotic leak was defined either by a positive radiographic finding on esophagram or by local examination due to clinical concern. Conduit ischemia was determined by the surgeon and defined by pale-blue or necrotic mucosal changes on visual or endoscopic examination of the tissue. Anastomotic strictures in the absence of recurrent disease were identified by symptomatic dysphagia with radiographic or endoscopic confirmation requiring endoscopic dilation. Cutaneous fistula was defined as a break in the epidermis with output consistent with gastrointestinal fluid or oral secretions.

Secondary outcomes included overall postoperative morbidity. This was defined as any of the following postoperative complications: respiratory/cardiac/renal/gastrointestinal complication or failure, deep venous thrombosis, surgical site infection, bleeding/thrombotic complication, mechanical ventilation > 48 h, or intensive care unit transfer.

Patients who underwent IC were compared to those who did not (NIC). Categorical variables were analyzed using chi square test with a Fischer's exact test for variable counts less than five. *T* tests were used for continuous variables. A p value of less than 0.05 was considered significant. Factors that were significant in the univariate analysis were entered into a multivariate logistic regression model. Statistical analysis was completed in the SAS System® package for Windows (Version 9.4, Cary, NC).

Results

Overall Patient Cohort

Demographic data are shown in Table 1. Two hundred seven patients met study criteria. One hundred seventy-two patients (83.1%) were male and the average age in the overall study was 65 years (range 24–82) with a mean body mass index (BMI) of 27 kg/m^2 (range 15.6–46). Sixty-one patients (29.5%) never used tobacco while 128 (61.8%) were former users and 18 (8.7%) patients were active users at the time of referral for an average of 21.4 pack-years (range 0–165).

Table 1 Demographic data for the study cohort

	Ischemic conditioning (IC) *n* = 38	No schemic conditioning (NIC) *n* = 169	*p* value
Males *n* (%)	29 (76.3)	139 (82.3)	0.398
Age mean [range] (years)	64.3 [49.8–79.4]	65.8 [24.3–82.7]	0.747
Active smokers *n* (%)	7 (18.4)	0 (0)	< 0.001
BMI mean [range] (kg/m^2)	24.0 [18.7–34.3]	26.5 [15.6–46.0]	0.002
Diabetes *n* (%)	3 (7.9)	37 (21.9)	0.048
Hypertension *n* (%)	18 (47.4)	91 (53.8)	0.825
Vascular disease *n* (%)	4 (10.5)	18 (10.7)	0.982
Charlson Comorbidity Index mean (SD)	4.6 (1.6)	4.7 (1.9)	0.746
Albumin (g/dl) mean (SD)	3.3 (0.55)	3.8 (2.5)	0.218
Benign disease *n* (%)	1 (2.6)	12 (7.1)	0.896
Achalasia *n* (%)	1 (2.6)	8 (4.7)	
End stage reflux *n* (%)	0 (0)	1 (0.6)	
Stricture *n* (%)	0 (0)	1 (0.6)	
Esophageal atony *n* (%)	0 (0)	2 (1.2)	
Malignant disease *n* (%)	37 (97.4)	158 (93.5)	0.896
High-grade dysplasia *n* (%)	0 (0)	6 (3.6)	0.595
Adenocarcinoma *n* (%)	33 (86.8)	132 (78.1)	
Stage I *n* (%)	1 (3)	28 (21.2)	
Stage II *n* (%)	13 (39.4)	41 (31.1)	
Stage III *n* (%)	19 (57.6)	59 (44.7)	
Stage IV *n* (%)	0 (0)	0 (0)	
Squamous cell carcinoma *n* (%)	4 (10.5)	19 (11.2)	
Stage I *n* (%)	0 (0)	2 (10.5)	
Stage II *n* (%)	0 (0)	3 (15.8)	
Stage III *n* (%)	4 (100)	14 (73.7)	
Stage IV *n* (%)	0 (0)	0 (0)	
Neoadjuvant Therapy *n* (%)	36 (94.7)	121 (71.6)	
Radiation *n* (%)	36 (94.7)	120 (71.0)	0.001
Chemotherapy *n* (%)	36 (94.7)	121 (71.6)	0.001

BMI body mass index

Thirteen patients (6.3%) underwent esophagectomy for benign diagnoses. The remaining 194 patients had cancer (79.7% adenocarcinoma, 11.1% squamous cell carcinoma) or high-grade dysplasia (2.9%). The average Charlson Comorbidity Index was 4.7 (range 0–11). Operative data are shown in Table 2. Most patients in both groups underwent a minimally invasive three-field (McKeown) resection with a staple cervical anastomosis. The mean follow-up time in the study population was 19 months. Eight patients were lost to follow-up.

Ischemic Conditioning

Thirty-eight patients (18.4%) underwent ischemic conditioning prior to esophagectomy. The average time from IC to esophagectomy was 98 days (range 11–205). The mean BMI was significantly higher in the NIC group ($p = 0.002$), while diabetes was statistically less common in the IC group ($p = 0.048$, Table 1). The incidence of other comorbidities, as well as the mean age-adjusted Charlson Comorbidity Index, was similar between the two groups. Only one patient who underwent IC had benign disease (achalasia) compared to 12 patients (7.1%) in the NIC group. Most patients in the IC group with malignancy underwent neoadjuvant chemoradiotherapy (CRT), while significantly less of the NIC group had CRT (95 vs. 71%, $p = 0.001$). There was no difference in the amount of lymph nodes harvested during esophagectomy between the IC group (mean 22.1, SD 8.9) compared to the NIC group (mean 21.2, SD 10.8, $p = 0.62$) (Table 2).

Table 2 Operative data for the study cohort

	Ischemic conditioning (IC) $n = 38$	No ischemic conditioning (NIC) $n = 169$	p value
Surgical approach	*38*	169	0.700
Minimally invasive n (%)	37 (97.4)	159 (94.1)	
Open n (%)	1 (2.6)	9 (5.3)	
Hybrid n (%)	0 (0)	1 (0.6)	
Anastomosis type	38	169	0.104
Stapled n (%)	35 (92.1)	158 (93.5)	
Hand sewn n (%)	2 (5.3)	11 (6.5)	
Discontinuity n (%)	1 (2.6)	0 (0)	
Anastomosis location	38	169	0.105
Chest n (%)	3 (7.9)	12 (7.1)	
Neck n (%)	34 (89.5)	157 (92.9)	
Discontinuity n (%)	1 (2.6)	0 (0)	
Lymph nodes harvested mean (SD)	22.1 (8.9)	21.2 (10.8)	0.620

Postoperative Outcomes

The incidence of overall morbidity after esophagectomy in the IC group was 36.8% compared to 56.2% in the NIC group ($p = 0.031$) (Table 3). The most common morbidity in both groups was related to pulmonary complications (pneumonia and respiratory failure), although rates of individual complications did not differ between groups.

Only 13.2% of the IC group experienced any type of anastomotic complication, compared to 33.7% in the NIC group ($p = 0.011$). There was no significant difference in anastomotic leaks (IC 7.9 vs. 5.3%, $p > 0.05$), cutaneous fistula formation (IC 0 vs. 1.8%, $p > 0.05$), and ischemic conduit (IC 0 vs. 2.4%, $p > 0.05$) between groups. There was a significant fourfold reduction in postoperative strictures in the IC group as compared to the NIC group (5.3 vs. 20.7%, $p =$ 0.025).

Logistic regression modeling was performed to include the variables with a significant association in the univariate analysis as well as those considered clinically important (Table 4). IC was significantly associated with reduced overall morbidity on logistic regression (OR 0.41, 95% CI 0.18–0.89). IC and postoperative strictures were not statistically significant (OR 0.41, 95% CI 0.07–2.30). Overall, nine patients in the study

Table 3 Postoperative outcomes for the study cohort

	Ischemic conditioning (IC) $n = 38$	No ischemic conditioning (NIC) $n = 169$	p value
Overall morbidity n (%)	14 (36.8)	95 (56.2)	0.031
Pneumonia n (%)	4 (10.5)	20 (11.8)	1.000
Respiratory failure n (%)	3 (7.9)	21 (12.4)	0.580
Surgical site infection n (%)	3 (7.9)	14 (8.3)	1.000
Chylothorax n (%)	1 (2.6)	8 (4.7)	1.000
Pulmonary embolism n (%)	0 (0)	3 (1.8)	1.000
Stroke n (%)	0 (0)	2 (1.2)	1.000
Renal failure n (%)	2 (5.3)	2 (1.2)	0.160
Myocardial infarction n (%)	0 (0)	1 (0.6)	1.000
Anastomotic complications n (%)			0.011
Anastomotic leak n (%)	3 (7.9)	9 (5.3)	0.226
Cutaneous fistula n (%)	0 (0)	3 (1.8)	0.542
Ischemic conduit n (%)	0 (0)	4 (2.4)	0.441
Staged procedure/discontinuity n (%)	1 (2.6)	6 (3.6)	0.385
Stricture n (%)	2 (5.3)	35 (20.7)	0.025
Stricture			
Number of dilations mean [range]	2.5 [1–4]	3.3 [1–12]	0.714

Table 4 Logistic regression analysis of morbidity and strictures

	Morbidity		Stricture	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age (years)	1.05 (0.99, 1.10)	0.06	1.02 (0.91, 1.12)	0.77
Gender (female)	0.66 (0.29, 1.51)	0.33	2.89 (0.50, 16.70)	0.24
ASA score	0.55 (0.13, 2.44)	0.76	0.16 (0.03, 1.01)	0.98
CCI	1.06 (0.83, 1.37)	0.63	1.16 (0.72, 1.88)	0.53
Diabetes	1.34 (0.58, 3.11)	0.47	0.39 (0.06, 2.34)	0.30
Benign (vs. malignant) disease	0.80 (0.30, 2.10)	0.65	7.06 (1.06, 46.97)	0.04
Surgical approach (MIS vs. open)	0.14 (0.02, 1.21)	0.07	0.001 (0.001, 1000)	0.98
Ischemic conditioning	0.41 (0.18, 0.89)	0.02	0.41 (0.07, 2.30)	0.31
Neoadjuvant CRT	2.10 (0.90, 4.93)	0.09	1000 (0.001, 1000)	0.99

ASA American Society of Anesthesiology, *CCI* Charlson Comorbidity Index, *MIS* minimally invasive surgery, *CRT* chemoradiotherapy

(4.3%) died within 30 days of operation. Three were in the IC group (7.9%) and six in the NIC group (3.6%) ($p = 0.37$).

Discussion

Despite advancements in the care of esophageal disease, esophagectomy remains a morbid procedure owing to the extent of dissection, magnitude of organ resection, and construction of a, sometimes, tenuous esophagogastric anastomoses. Our study suggests that preoperative gastric ischemic conditioning may play a role in the mitigation of some of the complications related to the procedure.

Anastomotic complications such as conduit ischemia, anastomotic leak, stricture, and fistulization may all share a common etiology of poor microperfusion to the site of anastomosis. Akiyama and colleagues[7] were one of the first groups to study techniques for improving gastric cardia blood flow prior to esophagectomy and esophagogastric anastomosis in humans. They embolized the left gastric, right gastric, and splenic arteries in 54 patients. Blood flow was then measured through a laser flow meter and the embolized group was compared to 25 control patients. Anastomotic leakage occurred in 2% of the embolization group versus 8% of controls. Subsequent studies have demonstrated improved anastomotic and mucosal blood flow and microvasculature, reduced collagen deposition and inflammation, and increased muscularis propria preservation after gastric conditioning.[9,15–17] However, despite these findings, actual clinical outcomes data have been mixed.

A recent comprehensive review of ischemic conditioning included 16 clinical studies along with a meta-analysis of 12 comparative studies.[10] The authors concluded that IC has promising results with regard to reducing the incidence and severity of anastomotic leak; however, pooled analysis was unable to demonstrate statistically significant differences. Much of clinical studies to date have not shown a reliable benefit in the reduction of anastomotic complications.[10,12] Furthermore, the majority of studies have focused solely on the reduction of anastomotic leaks, at the exclusion of other anastomotic or procedure-related complications.

Other investigators have performed a meta-analysis of factors affecting anastomotic integrity.[11] They examined 12 studies compromising 1215 patients comparing IC to control groups. The results showed a reduced rate of anastomotic leak in the IC group, although this did not reach statistical significance. Of these studies, only one paper analyzed anastomotic complications other than leaks. This group retrospectively studied 81 patients who underwent IC, compared to 71 patients who did not.[18] There were no statistical differences between these two groups with regard to outcomes. What is notable, however, is that the IC group had a greater proportion of anastomotic leaks and stricture, in addition to major and minor complications.

Our current series of 207 consecutive esophagectomy cases supports the prior literature regarding the safety and feasibility of laparoscopic ischemic conditioning. Furthermore, we demonstrated that ischemic conditioning is associated with less overall anastomotic complications and rates of postoperative stricture. The IC group had statistically fewer overall anastomotic complications. However, our cohort did not demonstrate a significant reduction in anastomotic leak (Table 3). These findings parallel much of the established literature in demonstrating that a significant reduction in anastomotic leaks has not realized across studies.

In our current study, ischemic conditioning was statistically associated with a fourfold reduction (5.3 vs. 20.7%, $p = 0.025$) in postoperative strictures. More interestingly, patients who had IC required, on average, fewer dilations than those who did not undergo IC, although this difference did not achieve statistical significance. Our findings contrast with a previous study demonstrating a 30% stricture rate after IC and a 25% stricture rate without IC.[18]

We have shown that ischemic conditioning is a safe adjunctive procedure that may be associated with reduced anastomotic complications and postoperative strictures after esophagectomy. These reductions could be explained by a few factors. As previously demonstrated, selective ligation of a proportion of the gastric blood supply causes hypertrophy, dilation, and neovascularization of the remaining feeding vessel that improves blood flow to the future site of conduit anastomosis and an associated increased tissue oxygenation.[7,9,15–17] These findings indicate a protective effect on the anastomosis during critical initial healing time subsequently reducing the risk of these complications. This may explain the reduction of overall anastomotic complications. Another possible explanation for improved anastomotic outcomes postoperative morbidity is that the gastric conduit is mobilized during IC and a feeding jejunostomy is also placed, and both of these interventions reduce the overall operating time during the subsequent esophagectomy. Additionally, during subsequent esophagectomy, the stomach does not need to be manipulated to same extent that a non-IC stomach does which is less traumatic to the future conduit.

Many of our patients who underwent IC had preoperative feeding tubes placed due to their inability to tolerate oral intake due to an obstructing cancer. This contrasts with patients who did not have dysphagia or an obstructing cancer that were able to tolerate some degree of oral intake, but may not have benefited from full nutritional optimization by enteral formula feeding. Despite this difference, preoperative albumin values were similar between groups, which suggests both groups may have had similar nutritional statuses prior to esophagectomy. Furthermore, a significantly higher proportion of IC patients underwent neoadjuvant CRT. This parallels the fact that the IC group had overall higher stage disease among patients with adenocarcinoma or squamous cell carcinoma. Given this, one might expect the IC group to have poorer outcomes in comparison; however, improved outcomes were seen in the IC group. In selecting higher risk patients, it could be hypothesized that this group would more likely have a statistically increased rate of anastomotic leaks and the lack of a statistical difference in this cohort is suggestive of the protective nature of IC.

There are a few limitations to this study. Since this study was not randomized, there is a selection bias, which may contribute to reduced complications seen in the IC group. IC patients were selected based on clinical suspicion for higher risk of poor anastomotic perfusion (tobacco use, diabetes), cardiovascular disease, or inability to tolerate oral intake due to an obstructing cancer, all markers for high-risk comorbid illness and advanced cancer. As a result, one would expect worse outcomes in this group, though this study did not demonstrate these adverse outcomes. Though obesity and poorly controlled diabetes were considered for ischemic conditioning, there was a higher prevalence in the NIC group. This outcome may be due to patients having met only one criterion for selection (diabetic, though normal BMI, non-smoker, no need for jejunostomy tube) and thus did not undergo ischemic conditioning. Lastly, eight patients were completely lost to follow-up. These patients may have experienced anastomotic complications after they were lost to follow-up that may have biased the data for the small number of patients in the IC group. However, this is infrequent at a tertiary care referral center with established long-term relationships throughout the region.

Conclusion

Gastric ischemic conditioning may decrease postoperative stricture rates and overall anastomotic morbidity after esophagectomy. It is not known which patients would most benefit from ischemic conditioning. Prospective, multi-center studies are needed to determine optimal ischemic conditioning selection criteria for patients undergoing esophagectomy.

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