Randomized Controlled Trial

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Pilot Trial on Ischemic Conditioning of the Gastric Conduit in Esophageal Cancer: Feasibility and Impact on Anastomotic Leakage (TIGOAL-I)

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Objective: To evaluate the feasibility, safety, and effectiveness of gastric conditioning using preoperative arterial embolization (PAE) before McKeown esophagectomy at a tertiary university hospital.

Background: Cervical anastomotic leakage (AL) is a common complication of esophagectomy. Limited clinical evidence suggests that gastric conditioning mitigates this risk.

Methods: This pilot randomized clinical trial was conducted between April 2016 and October 2021 at a single-center tertiary hospital. Eligible patients with resectable malignant esophageal tumors, suitable for cervical esophagogastrostomy, were randomized into 2 groups: one receiving PAE and the other standard treatment. The primary endpoints were PAE-related complications and incidence of cervical AL.

Results: The study enrolled 40 eligible patients. PAE-related morbidity was 10%, with no Clavien-Dindo grade III complications. Cervical AL rates were similar between the groups (35% *vs* 25%, $P = 0.49$), even when conduit necrosis was included (35% *vs* 35%, $P = 1$). However, AL severity, including conduit necrosis, was higher in the control group according to the Clavien-Dindo ≥IIIb (5% *vs* 30%, $P = 0.029$) and Comprehensive Complication Index (20.9 *vs* 33.7, $P = 0.01$). No significant differences were found in other postoperative complications, such as pneumonia or postoperative mortality.

Conclusions: PAE is a feasible and safe method for gastric conditioning before McKeown minimally invasive esophagectomy and shows promise for preventing severe AL. However, further studies are required to confirm its efficacy.

Keywords: anastomotic leak, esophageal cancer, gastric conditioning, McKeown

INTRODUCTION

Despite numerous advances in esophageal cancer surgery, cervical anastomotic leakage remains a significant postoperative complication after esophagectomy.[1] Minimally invasive esophagectomy (MIE) has demonstrated superiority over open esophagectomy in terms of postoperative outcomes.[2] Nevertheless, cervical leak rates of up to 34.1% have been reported after MIE.[3]

Anastomotic leak (AL) is a multifactorial complication that is influenced by patient factors, underlying diseases, and technical aspects. Notably, compromised gastric conduit perfusion is a major risk factor for AL.[4–6] Consequently, strategies to enhance gastric perfusion have been proposed. Gastric conditioning (GC) involves surgical ligation or percutaneous embolization of vessels supplying the stomach before esophagectomy, relying solely on the right gastroepiploic artery (RGeA) for perfusion.[7] Experimental and clinical studies have demonstrated improved tissue perfusion and neovascularization of the gastric submucosa following laparoscopic or arteriographic GC, with peak effects observed after 14 days.[8–10]

However, current evidence has yielded conflicting results. Preoperative arterial embolization (PAE) for GC appears to reduce the AL rate in some studies,[11] while others have reported similar rates.[12] Importantly, these studies have not adequately dissected the role of arteriographic GC in cervical and thoracic anastomoses.

Cervical anastomosis has been linked to a higher AL incidence compared to intrathoracic anastomosis.[13–15] Theoretically, patients undergoing McKeown surgery may benefit more from preoperative GC than those undergoing Ivor-Lewis esophagectomy. Based on these considerations, the aim of this study was to evaluate the feasibility, safety, and efficacy of PAE before total or hybrid minimally invasive McKeown esophagectomy for esophageal cancer patients. To the best of our knowledge, no published randomized clinical trials have directly compared the outcomes of GC with PAE against the conventional approach for McKeown esophagectomy.

METHODS

This pilot parallel open-label randomized clinical trial was conducted at a tertiary academic medical center, Hospital Clínico Universitario, Valencia. This study evaluated several primary

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endpoints, including complications related to PAE, time between preoperative treatment and surgery, and AL rate. Secondary endpoints, such as overall postoperative complications, were also assessed. The study was registered as NCT04268654 on ClinicalTrials.gov and the protocol was approved by our ethics committee. Written informed consent was obtained from all patients.

Patients

Between April 2016 and October 2021, all patients aged >18 years with a Karnofsky performance status >50% and having a resectable esophageal malignant tumor eligible for esophagectomy with cervical esophagogastrostomy were assessed for trial inclusion. Exclusion criteria were: (1) metastatic disease, (2) anatomic vascular alterations (congenital celiac trunk stenosis, presence of arcuate ligament or atherosclerotic stenosis), (3) severe cardiorespiratory failure, and (4) refusal to participate in the study.

Randomization

Patients were randomly assigned to either the control group (no-PAE) or the experimental group (PAE) using a 1:1 allocation ratio through a web-based centralized permuted block randomization system. Owing to the nature of the intervention, neither the operator nor the subjects could be blinded. Patients who met the inclusion criteria and provided informed consent were randomized into 1 of 2 arms. The randomization list was prepared by the INCLIVA Health Research Institute statistician, who had no clinical involvement in the trial. Treatment allocations were sealed in numbered envelopes, which were subsequently opened in the surgeon's clinic after the patient signed the informed consent form.

Control Group

Patients in both treatment arms received the same protocolized pre- and postoperative care. The study duration was from the randomization visit to 90 days after surgery. Preoperative evaluations included endoscopy with biopsy to confirm tumor histology, thoracic and abdominal computed tomography (CT), positron emission tomography, and ultrasonographic endoscopy. Patients were staged according to the clinical TNM classification (8th edition). Neoadjuvant chemoradiotherapy or chemotherapy was administered to patients with ≥T2 and/or N+ tumors. The respiratory prehabilitation program and nutritional assessments were performed preoperatively in all patients.

The surgeries were performed by 2 expert surgeons from the esophagogastric surgery unit of the hospital (F.L.M. and R.M.O.). McKeown esophagectomy was performed using the thoracoscopic approach in the prone position. After completing the thoracoscopic procedure, the patient was rotated to the dorsal decubitus position, with the neck extended and turned toward the right. Two-field lymphadenectomy was performed in all cases. In general, standard lymphadenectomy was performed for tumors located in the lower third of the stomach, while extended lymphadenectomy was performed for tumors located in the middle third, taking into account the N stage. The extent of dissection was increased to total lymphadenectomy depending on the lymph node involvement observed in imaging tests and the histological type of the tumor. The abdominal approach was performed laparoscopically or via laparotomy. Despite the abdominal surgical approach, all patients underwent Akiyama tube reconstruction. The gastric conduit was constructed with multiple firings of a 75-mm linear cutter along the lesser curvature. The staple line was not inverted. No pyloromyotomy or pyloroplasty was carried out. The stomach was raised to the neck through the posterior mediastinal route. Cervical anastomosis was performed by an end-to-side hand-sewn technique. A chest tube and a cervical drain were inserted. Feeding jejunostomy was not performed.

Postoperatively, all patients were examined for AL using methylene blue administered orally on postoperative days 3–5. In the event of a positive test indicated by blue dye staining the cervical drain, an endoscopy and/or CT scan with oral water-soluble contrast was performed to evaluate the anastomosis and rule out conduit necrosis. If the methylene blue test result was negative, oral intake was started, and the test was repeated in case of any clinical changes such as fever, changes in the drains or cervical wound erythema, and the appearance of respiratory complications.

Intervention

PAE was performed in the experimental group by 2 expert interventional radiologists from the hospital (J.G.R. and E.C.), 3 weeks before esophagectomy. The procedure consisted of arteriographic embolization of 3 arteries (left gastric artery [LGA], right gastric artery [RGA], and splenic artery [SpA]), leaving the RGeA patent.

Before and after the procedure, a celiac trunk angiogram was performed via femoral access to identify possible anatomical variations in the celiac trunk before embolization (Fig. 1). Embolization in the proximal SpA was primarily performed with vascular occlusion devices (Amplatzer Vascular Plug, Abbott Cardiovascular), and if technical difficulties arose, embolization was achieved with coils of varying calibers depending on the size of the artery (usually between 8 and 10 mm). Similarly, the LGA was primarily embolized with coils between 4 and 8 mm or vascular occluders placed in the main trunk before branching the artery. During the procedure, the left hepatic artery was assessed to rule out the presence of accessory gastric vessels that required embolization.

For selective embolization of the RGA, an antegrade microcatheter was inserted. If this approach was not feasible, retrograde catheterization was attempted across the arch on the lesser curvature with a microcatheter in the LGA as a guide. Microcoils were placed proximally in the artery (from the main trunk to the first branch point). Final celiac angiography confirmed both embolization and the absence of gastric blood supply from arteries other than the RGeA (Fig. 2).

The patients were allowed to resume food intake immediately after the procedure and were discharged the following day if they did not experience nausea, abdominal pain, or fever.

Outcome Measures

The primary outcomes were the feasibility, safety, and efficacy of PAE. Multiple variables were meticulously assessed, including complete embolization rate, delay in surgical treatment, morbidity associated with PAE, and cervical AL rate.

Complete embolization was deemed to be achieved when all 3 arteries (LGA, RGA, and SpA) were effectively embolized, incomplete technique when 1 or 2 arteries were embolized, and technique failure when no artery was embolized. The time from the initiation of preoperative treatment to surgery was also analyzed. To gauge morbidity subsequent to PAE, we employed the Clavien-Dindo Classification[16] and Comprehensive Complication Index (CCI).[17]

AL was considered when one or more of the following conditions were met: drainage of esophagogastric content or methylene blue through the cervical drain, confirmed endoscopically, confirmed radiologically through a cervicothoracoabdominal CT scan with oral contrast, and/or confirmed by the surgeon during a reintervention. AL and conduit necrosis (CN) were characterized based on the classification developed by the esophagectomy complications consensus group.[18]

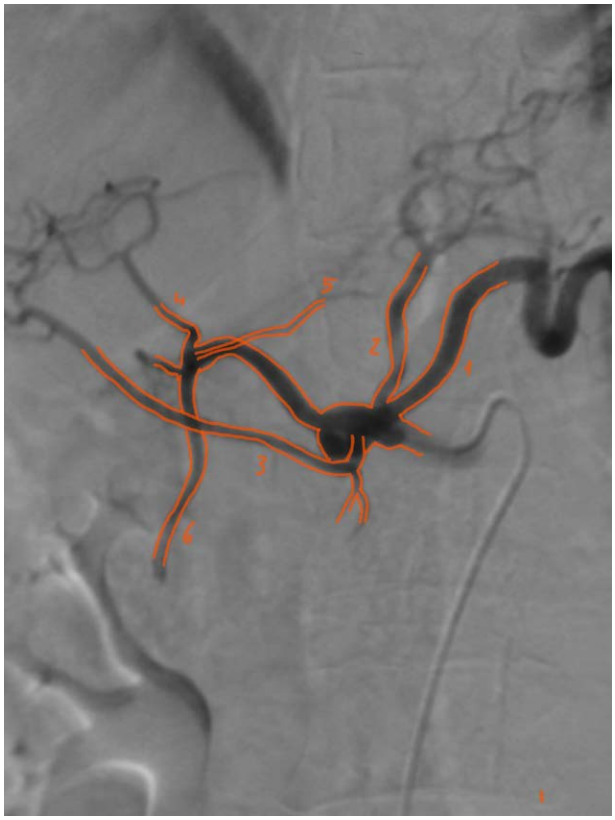

FIGURE 1. An anatomic variant in angiogram before embolization: right hepatic artery originating directly from the celiac trunk. 1: splenic artery; 2: left gastric artery; 3: right hepatic artery; 4: left hepatic artery; 5: right gastric artery; 6: gastroduodenal artery.

Secondary outcomes included additional postoperative complications, duration of hospitalization, intensive care unit stay, and mortality.

Statistical Analysis

Patient data were analyzed on an intention-to-treat basis. Categorical variables were expressed as count (percentage) and quantitative variables as mean standard deviation or median (25–75% interquartile range) unless otherwise specified. Continuous secondary variables were analyzed using the Student *t* test, categorical secondary variables using Fisher exact test, and ordinal variables using the Mann–Whitney *U* test. Data were analyzed using SPSS statistical software version 21.0 for Windows (IBM Corp., Armonk, NY, USA). The sample size was not determined because of the exploratory nature of the study.

RESULTS

Baseline Characteristics

Between April 2016 and October 2021, 49 patients were screened for participation in the trial, and 40 patients finally participated (Fig. 3). Among the 40 randomized patients, 20 underwent PAE (experimental group), and 20 were allocated to the control group. The baseline demographics and operative characteristics are summarized in Table 1 and were similar between the treatment groups. The final date of follow-up data collection was January 2022.

Feasibility and Safety of PAE

Twenty patients were randomized to undergo PAE before esophagectomy. Complete PAE was achieved in 18 of the 20 patients (90%). In the remaining 2 patients, the RGA was not occluded. The time interval between preoperative treatment and surgery was comparable between the PAE and non-PAE groups (4 [3–4] months *vs* 3 [3–4] months; $P = 0.43$). Complications were observed in 2 patients (10%), classified as Clavien-Dindo grade I: one case of inguinal hematoma and another patient with fever occurring within 24 hours postprocedure. No readmissions occurred. Regarding the surgical aspect, the operative time did not significantly differ in the PAE group ($P = 0.24$, Table 1). The laparoscopic approach rate was similar between the PAE and control groups (45% *vs* 35%; $P = 0.51$), with no conversions observed in either group.

Anastomotic Leakage

The overall incidence of AL was 35% in the PAE group and 25% in the control group (risk difference, 1.61% [95% CI, 0.41–6.33]). Notably, both the CN cases were concentrated in the control group (Table 2). By combining AL and CN, the severity of leakage was higher in the control arm, as indicated by both the Clavien-Dindo and CCI scores (Table 2).

Among the 7 patients with AL in the PAE group, 6 were successfully managed with conservative measures, while the

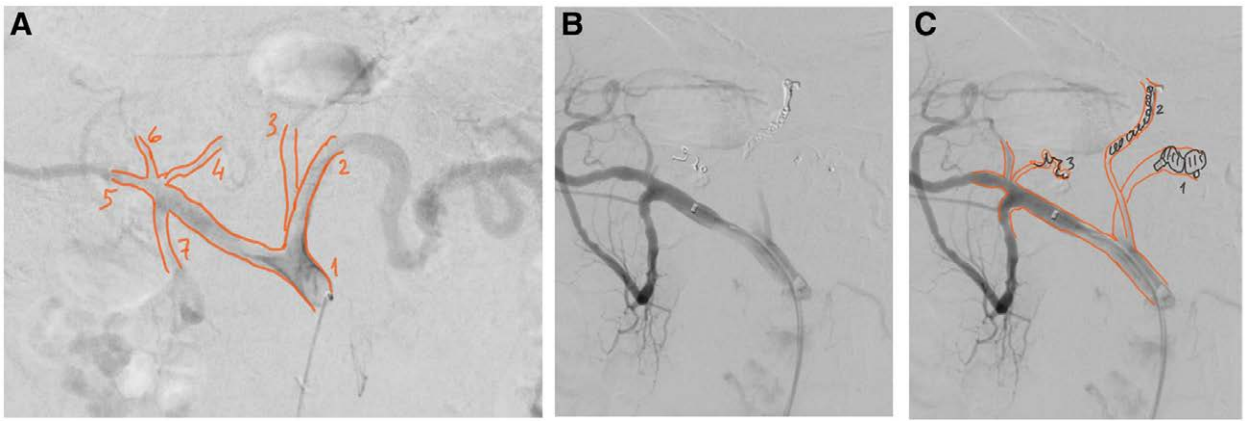

FIGURE 2. Gastric embolization: (A) angiogram before embolization. (B) Angiogram after embolization. (C) Description of the methods used for embolization. A, 1: celiac trunk; 2: splenic artery; 3: left gastric artery; 4: right gastric artery; 5: right hepatic artery; 6: left hepatic artery; 7: gastroduodenal artery. B, Angiogram confirming the absence of arterial flow through the embolized vessels. C, 1: amplatzer occluder device in splenic artery; 2: microcoils in left gastric artery before bifurcation; 3: microcoil at the origin of the right gastric artery.

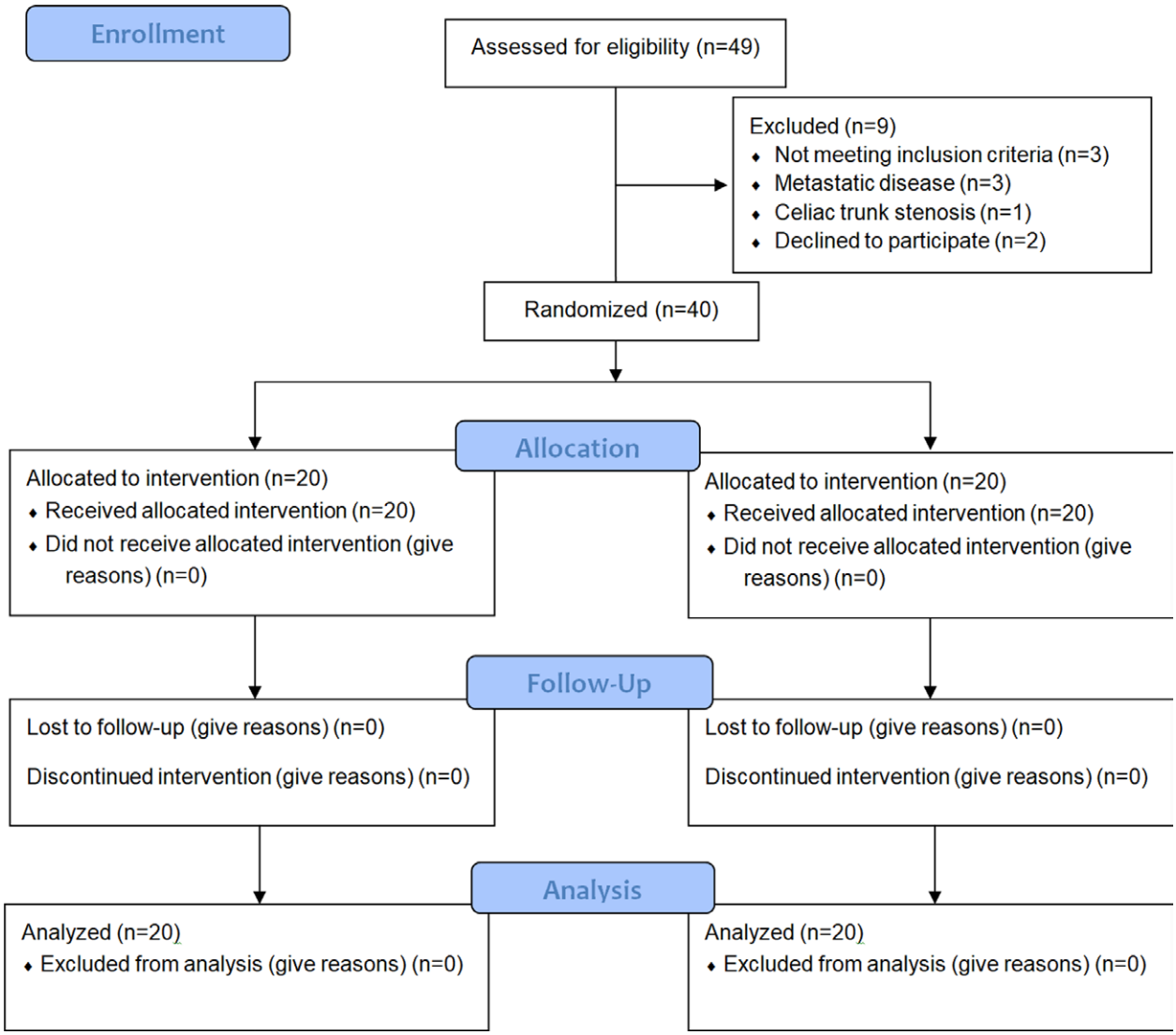

FIGURE 3. CONSORT flow diagram.

remaining patient required surgery after stent treatment failed. In the control arm, 3 of 7 patients with AL were managed conservatively, 2 were treated with a stent, and 2 underwent surgery for type III CN. The surgical procedure involved the removal of the gastric conduit, cervical esophagostomy, and the creation of a feeding jejunostomy.

All cases of dehiscence were identified using an oral methylene blue test. However, 10% of AL were diagnosed early, and the methylene blue test on day 3 was positive in all cases. In the remaining cases of AL, the test result was positive at the time of administration. Endoscopic evaluation demonstrated no defects or punctate anastomotic defects in 64.2% (9/14) of cases and CN in 2 cases.

General Complications

A total of 22 out of 40 (55%) patients developed complications. Clavien IIIb or higher complications occurred in 22.5% (9/40) of the patients, and the rate of pulmonary complications was 35% (15/40). Table 3 shows the postoperative morbidity according to the treatment group. There were no differences between the groups in the rates of postoperative morbidity, severity of complications, or length of postoperative hospital stay. The ninety-day mortality rate of the entire series was 2.5%.

DISCUSSION

This study represents one of the first randomized clinical trials assessing PAE in patients with esophageal cancer undergoing McKeown esophagectomy. The study aims to ascertain the safety of this technique, evaluate its feasibility in a tertiary hospital setting, and delineate the expected outcomes.

The APIL-13 trial[19] recently investigated the application of PAE in Ivor-Lewis esophagectomy, reporting an 86.4% complete embolization rate and a 22.7% morbidity rate. Our study achieved a comparable complete gastric embolization rate of 90%, and notably, with a complication rate of 10%. Complications related to coil migration, such as pancreatitis or cholecystitis, and arterial dissections have been described.[11,19] However, it is noteworthy that none of these complications occurred among the patients in the experimental group.

PAE presents a higher rate of splenic infarction, attributed to the inability to achieve selective embolization of short gastric vessels. This complication has been described in approximately 40% of cases when a CT was performed a week before surgery.[11] In our study, confirmation of splenic infarction with CT post-PAE was not included in the study protocol because it is typically a clinically insignificant finding.

Recently, the ISCON trial reported no Clavien-Dindo grade ≥ II complications for laparoscopic GC. However, adherences were noted in 45% of cases, with severe adherences at 10%

TABLE 1.

Baseline Demographics and Operative Characteristics

	PAE (n = 20)	No-PAE (n = 20)	*P*
Age, mean (SD)	61 (9.9)	60 (9.3)	0.75
Sex, men: women	18:2	17:3	1
BMI, mean (SD)	25.65 (5.2)	26.85 (6.8)	0.53
ASA group			0.74
I–II	7 (35%)	8 (40%)	
III–IV	13 (65%)	12 (60%)	
Charlson Comorbidity Index score, median (IQR)	3 (1–5)	2 (1–3)	0.16
Comorbidities			
DM	5 (25%)	4 (20%)	1
Cardiovascular or respiratory disease	6 (30%)	5 (25%)	1
Renal disease	2 (10%)	0 (0%)	0.40
Liver disease	1 (5%)	3 (15%)	0.61
Thrombopathia	2 (10%)	1 (5%)	1
Cardiovascular risk factors	14 (70%)	10 (50%)	0.19
Preoperative serum albumin (g/dL), mean (SD)	3.8 (0.5)	3.9 (0.4)	0.80
Tumor type			0.71
Adenocarcinoma	14 (70%)	16 (80%)	
Squamous cell carcinoma	6 (30%)	4 (20%)	
Tumor location			0.27
Midesophagus	7 (35%)	3 (15%)	
Distal esophagus/GEJ	13 (65%)	17 (85%)	
cStage			0.71
II	4 (20%)	6 (30%)	
III	16 (80%)	14 (70%)	
Preoperative CT/CT-RT	19 (95%)	17 (85%)	0.60
Operation type			0.43
Total MIE	9 (45%)	7 (35%)	
Hybrid MIE	11 (55%)	13 (65%)	
Operating time, median (IQR)	306 (267–369)	316 (272–386)	0.24
Mediastinal lymphadenectomy			0.19
Standard	10 (50%)	14 (70%)	
Extended/total	10 (50%)	6 (30%)	
Lymph nodes, median (IQR)			
Retrieved	22 (15–32)	16 (15–25)	0.12
Positive	0 (0–3)	0 (0–1)	0.11
pT 3–4	10 (50%)	8 (40%)	0.52
pN +	13 (65%)	8 (40%)	0.11

ASA indicates American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CT, chemotherapy; GEJ, gastroes junction; MIE, minimally invasive esophagectomy; PAE, preoperative arterial embolization; RT, radiotherapy.

postprocedure.[20] This is the primary advantage of PAE over the laparoscopic approach. PAE did not lead to adhesions in our patients, and no conversions were required; in fact, the surgical time was even shorter in the experimental group. The application of PAE did not result in any delays in curative surgery and facilitated a minimally invasive approach, emphasizing the feasibility and safety of PAE in a tertiary hospital setting.

Akiyama et al[10] described GC by arterial embolization and showed a decreased rate of AL in patients who underwent gastric PAE. While most published studies have shown a trend toward a decrease in leakage rates when compared to controls, they have failed to demonstrate statistical significance,[12,21,22] except for the study conducted by Ghelfi et al[11] However, these retrospective studies have several drawbacks, including

TABLE 2.

Detailed Outcomes of Patients with Anastomotic Leakage

	PAE (n = 20)	No-PAE (n = 20)	*P*
AL; ECCG definition	7 (35%)	5 (25%)	0.49
I	4 (30%)	2 (10%)	0.45
II	2 (0%)	3 (15%)	
III	1 (5%)	0 (0%)	
AL size (mm)	4.7	11	0.04
Time to AL diagnosis (days), mean (SD)	8.1 (2.5)	8.2 (2.3)	0.96
Conduit necrosis type III	0 (0%)	2 (15%)	0.48
AL and CN severity			
Clavien <IIIb	6 (30%)	1 (5%)	0.02
Clavien ≥IIIb	1 (5%)	6 (30%)	
CCI, median (IQR)	20.9 (20.9–29.6)	33.7 (33.5–71.3)	0.01
Days in ICU, median (IQR)	2 (1–5)	7 (3–8)	0.03

AL indicates anastomosis leakage; CCI, comprehensive complication index; CN, Conduit Necrosis; ECCG, esophagectomy complications consensus group; ICU, intensive care unit; PAE, preoperative arterial embolization.

TABLE 3.

Secondary Outcomes of Entire Cohort

	PAE (n = 20)	No-PAE (n = 20)	*P*
Overall morbidity	10 (50%)	12 (60%)	0.34
Pulmonary complications	5 (25%)	10 (50%)	0.10
Pneumonia	2 (10%)	1 (5%)	
Pleural effusion/pneumothorax	0 (0%)	4 (20%)	
Acute Respiratory Distress syndrome	1 (5%)	3 (15%)	
COPD exacerbation	2 (10%)	2 (10%)	
Clavien ≥IIIb	2 (10%)	7 (35%)	0.19
CCI, median (IQR)	25.2 (20.9–40.3)	33.7 (28–42.4)	0.13
Days in ICU, median (IQR)	1 (1–4)	3 (1–7.7)	0.30
Hospital stay, days, median (IQR)	15 (8.5–28.5)	14 (9–25.2)	1
Postoperative mortality	0 (0%)	1 (5%)	1

CCI indicates Comprehensive Complication Index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; PAE, preoperative arterial embolization.

heterogeneity in the patients included (eg, cervical/intrathoracic anastomosis), different numbers of occluded vessels, and lack of standardized reporting for postoperative complications. CN has been included in the definition of AL in most studies.

Five meta-analyses have compared GC, including laparoscopic and embolization approaches.[23–27] Three studies performed subgroup analyses concerning preconditioning techniques, and the role of PAE remains controversial. Kamaraj et al[23] showed that embolization is associated with significantly lower rates of AL than in controls. However, Heger et al[25] and Michalinos et al[26] did not reveal a statistically significant reduction in AL. In our clinical trial, there was no significant reduction in AL in the PAE group.

In our study, the AL rate was lower in the control group than in the PAE group. The percentage of patients with cardiovascular risk factors, comorbidities, American Society of Anesthesiologists >2, and higher Charlson Index scores was higher in the PAE group compared to the control group, although the difference was not significant. This may have influenced the results. It is noteworthy that, although there was a higher percentage of AL in the PAE group, the severity was lower.

Meta-analyses and reviews have also highlighted the role of GC in reducing the severity of leakage.[25,26,28] This is the first trial to show the benefit of PAE in reducing the severity of leakage using a standardized classification (CCI and Clavien-Dindo). Embolized patients with cervical AL presented with fewer associated complications and a lower need for critical care.

Kechagias et al[29] emphasized the importance of identifying preoperative predictive factors that may help better select patients for GC. Future studies should explore the potential role of PAE in selected patients.

This study has some limitations. First, the sample size is small. Nevertheless, the results of this pilot study lay the groundwork for future investigations. A potential direction for further research could involve calculating the sample size required to detect differences in the occurrence of severe anastomotic complications. Second, the single-center trial design may have limited its external validity. However, these trials offer a higher degree of procedural uniformity and a more homogeneous study population than might be expected from multicentre trials. Third, although the 30% AL rate can be considered high, similar rates have been reported in other randomized clinical trials, with cervical AL rates ranging from 31% to 42%.[3,30] The AL diagnosis protocol, inclusive definition, and careful data registration may have contributed to a more comprehensive study of AL rates. It is possible that the results were also influenced by the percentage of patients with an American Society of Anesthesiologists score greater than 2 (62.5%).

Nevertheless, this trial with standardized surgical techniques and ischemic conditioning protocols is the first randomized trial that provides important preliminary data on the use of PAE in esophageal cancer patients undergoing minimally invasive McKeown procedures and includes a precise definition of AL and CN.

In conclusion, PAE is a feasible and safe procedure that leads to MIE in patients with esophageal cancer. Although PAE did not reduce the overall rate of AL, it appeared to reduce its severity. Future research is needed to better define the role of PAE before esophagectomy.

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