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Abstract: Endoluminal vacuum therapy (EVT) is an accepted treatment for anastomotic leakage (AL) after esophagectomy. A novel concept is to use this technology in a preemptive setting, with the aim to reduce the AL rate and postoperative morbidity. Preemptive EVT (pEVT) was performed intraoperatively in 19 consecutive patients undergoing minimally invasive esophagectomy, immediately after completion of esophagogastrostomy. Twelve patients (63%) were high-risk cases with severe comorbidity. The EVT device was removed routinely three to six (median 5) days after esophagectomy. The endpoints of this study were AL rate and postoperative morbidity. There were 20 anastomoses at risk in 19 patients. One patient (5.3%) experienced major morbidity (Clavien-Dindo grade IIIb) unrelated to anastomotic healing. He underwent open reanastomosis at postoperative day 12 with pEVT for redundancy of the gastric tube and failure of transition to oral diet. Mortality after 30 days was 0% and anastomotic healing was uneventful in 19/20 anastomoses (95%). One minor contained AL healed after a second course of EVT. Except early proximal dislodgement in one patient, there were no adverse events attributable to pEVT. The median comprehensive complication index 30 days after surgery was 20.9 (IQR 0-26.2). PEVT appears to be a safe procedure that may have the potential to improve surgical outcome in patients undergoing esophagectomy.

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DISEASES OF THE ESOPHAGUS

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Original Article

Preemptive endoluminal vacuum therapy to reduce anastomotic leakage after esophagectomy: a game-changing approach?

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SUMMARY. **Endoluminal vacuum therapy (EVT) is an accepted treatment for anastomotic leakage (AL) after esophagectomy. A novel concept is to use this technology in a preemptive setting, with the aim to reduce the AL rate and postoperative morbidity. Preemptive EVT (pEVT) was performed intraoperatively in 19 consecutive patients undergoing minimally invasive esophagectomy, immediately after completion of esophagogastrostomy. Twelve patients (63%) were high-risk cases with severe comorbidity. The EVT device was removed routinely three to six (median 5) days after esophagectomy. The endpoints of this study were AL rate and postoperative morbidity. There were 20 anastomoses at risk in 19 patients. One patient (5.3%) experienced major morbidity (Clavien–Dindo grade IIIb) unrelated to anastomotic healing. He underwent open reanastomosis at postoperative day 12 with pEVT for redundancy of the gastric tube and failure of transition to oral diet. Mortality after 30 days was 0% and anastomotic healing was uneventful in 19/20 anastomoses (95%). One minor contained AL healed after a second course of EVT. Except early proximal dislodgement in one patient, there were no adverse events attributable to pEVT. The median comprehensive complication index 30 days after surgery was 20.9 (IQR 0–26.2). PEVT appears to be a safe procedure that may have the potential to improve surgical outcome in patients undergoing esophagectomy.**

KEY WORDS: **anastomotic leakage, complications, minimally invasive esophagectomy, outcome research.**

INTRODUCTION

Anastomotic leakage (AL) is a frequent and life-threatening complication after esophagectomy.[1,2] Patients with severe comorbidities are at increased risk.[3-5] The pathophysiology of AL is likely to be multifactorial and involves technical issues, local ischemia, bacterial superinfection, and inflammation.[6,7]

Therapeutic strategies for AL have evolved dramatically over the last years and interventional endoscopy has replaced surgical revision in most situations. In this context, endoluminal vacuum therapy (EVT) has become an important therapeutic tool. The ways in which EVT works involve continuous removal of secretions, improvement of interstitial edema and microcirculation, and induction of granulation. A number of retrospective studies have established proof of the EVT concept with excellent outcome and low complication rates.[8,9]

A novel idea is to use the EVT technology in a preemptive setting with the aim of preventing AL and reducing postoperative morbidity. In a recent case series, early EVT in patients without leak but with endoscopically proven anastomotic ischemia was effective in six of eight patients.[10] Likewise, in a live porcine model, intraoperative application of EVT in esophagogastric anastomoses with intentional 1 cm defects resulted in complete healing.[11] With this in

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Specific author contributions: Study design, performing the experiments, drafting the manuscript: Christoph Gubler; Study design, performing the experiments, drafting the manuscript: Diana Vetter; Performing the experiments, interpretation of data, critical revision of the manuscript: Henner M. Schmidt, Philip C. Müller, Bernhard Morell; Statistical analysis, interpretation of data, critical revision of the manuscript: Dimitri Raptis; Study design, performing the experiments, interpretation of data, drafting the manuscript: Christian A. Gutschow. All authors gave their final approval.

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Conflicts of interest: The authors declare that they have no conflict of interest.

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mind and considering the high incidence and deleterious effects of AL, we implemented *preemptive* EVT (pEVT) in patients undergoing esophagectomy and gastric tube reconstruction.

PATIENTS AND METHODS

From a prospectively maintained database, we identified 19 consecutive patients who underwent esophagectomy with intraoperative pEVD between November 2017 and May 2018 in our department. In our institution, we perform 25–30 esophagectomies per year with an AL rate of 8% over the last 50 cases before implementation of pEVT. Institutional review board approval was obtained (2018–01198).

Records of patients were reviewed with respect to demographic characteristics, oncological parameters, surgical procedures, and the postoperative course up to 90 days after surgery. The endpoints of this study were postoperative morbidity and AL rate, defined according to the Esophageal Complications Consensus Group (ECCG) (Table 1),[12] the Clavien–Dindo (CD) classification, and the comprehensive complication index (CCI).

Surgical technique and perioperative management

The surgical procedures were total (laparoscopic/thoracoscopic) minimally invasive Ivor Lewis esophagectomy (ttMIE) with high intrathoracic circular stapled end-to-side esophagogastrostomy ($n = 18$) and minimally invasive retrosternal gastric tube reconstruction with circular stapled end-to-side cervical esophagogastrostomy in a patient undergoing secondary reconstruction after esophagectomy ($n = 1$). In all cases, we created a double-stapled 25 mm circular anastomosis using the OrVil device (Medtronic, Minneapolis, USA). In addition, an omental wrap was placed routinely between the trachea and anastomosis. At the end of the procedure, two chest tubes (20 French) were inserted in the right hemithorax, one close to the anastomosis at the apex and one posterior-basal. Another basal thoracic drain was placed in the left chest. Feeding jejunostomies were inserted in high-risk situations or in patients with preoperative weight loss >10% only. Enteral nutrition was started over the jejunostomy on postoperative day 1 and advanced as tolerated, while a liquid oral diet was started after removal of the Eso-SPONGE. Antibiotic prophylaxis (Tazobac, Pfizer PFE GmbH, Zurich, Switzerland) was given routinely for 5–7 days.

Endoluminal vacuum therapy

Immediately after completion of the anastomosis, the Eso-SPONGE (an open-pored polyurethane sponge fitted to a gastric tube, B. Braun Melsungen AG, Melsungen, Germany) was placed endoscopically via an overtube. The central part of the sponge was positioned exactly at the level of the anastomosis. The tube was routed transnasally and then connected to a vacuum pump (Medela Thopaz, Medela Healthcare, Baar, Switzerland), generating a continuous negative pressure of 75 mmHg. The tube was marked and tape-fixed at the nostril to monitor and prevent dislocation. Throughout therapy, the Eso-SPONGE system was checked 6-hourly for leakage and dislocation. The sponge was removed after 4 to 6 days via gastroscopy. The timing of the endoscopic sponge extraction varied due to the limited availability of our endoscopy service for routine procedures on weekends. After removal, the anastomosis and the gastric tube were assessed endoscopically to exclude leakage or ischemia, and the pylorus was evaluated for spasm. Repeat endoscopy, contrast radiography, or computed tomography to exclude late AL was performed according to the further clinical course.

Table 1 Patient characteristics ($n = 19$)

Age, years (median, IQR)	66 (62–71)
BMI, kg/m^2 (median, IQR)	27.1 (24.6–30.6)
Male, *n* (%)	18 (95)
WHO/ECOG performance status, *n* (%)	
Grade 0	7 (37)
Grade I	10 (53)
Grade II	2 (11)
ASA status, *n* (%)	
Grade I–II	8 (31)
Grade III	10 (61)
Grade IV	1 (8)
Charlson comorbidity index (median, IQR)	3 (2–5)
Histology, *n* (%)	
AC	15 (79)
SCC	3 (16)
Benign	1 (5)
Tumor location, *n* (%)*	
Proximal half of esophagus	3 (16)
Distal half of esophagus	11 (58)
Esophagogastric junction (Siewert II)	4 (21)
Preoperative therapy, *n* (%)*	
None	6 (50)
Radiochemotherapy	11 (58)
Chemotherapy	1 (5)
Surgical approach	
Laparoscopic/thoracoscopic Ivor Lewis	18 (92)
Retrosternal gastric tube reconstruction	1 (8)
Reanastomosis for redundant gastric tube	1 (8)
UICC stages, *n* (%)*	
I	5 (27.8)
Ia	1(5.6)
Ib	2(11.1)
II	3 (16.7)
IIIA	3 (16.7)
IIIB	3 (16.7)
Iva	1 (5.6)

*Patients with malignant indication $n = 18$.
IQR, interquartile range; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; ASA, American Society of Anesthesiologists; AC, adenocarcinoma; SCC, squamous cell carcinoma; UICC, Union Internationale Contre le Cancer TNM Classification for Esophageal Cancer 8th edition.

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Table 2 Anastomotic leak defined according to the Esophageal Complications Consensus Group[12]

Definition: Full-thickness gastrointestinal defect involving esophagus, anastomosis, staple line, or conduit irrespective of presentation or method of identification	
Type I	Local defect requiring no change in therapy or treated medically or with dietary modification
Type II	Localized defect requiring interventional but not surgical therapy, for example, interventional radiology drain, stent or bedside opening, and packing of incision
Type III	Localized defect requiring surgical therapy

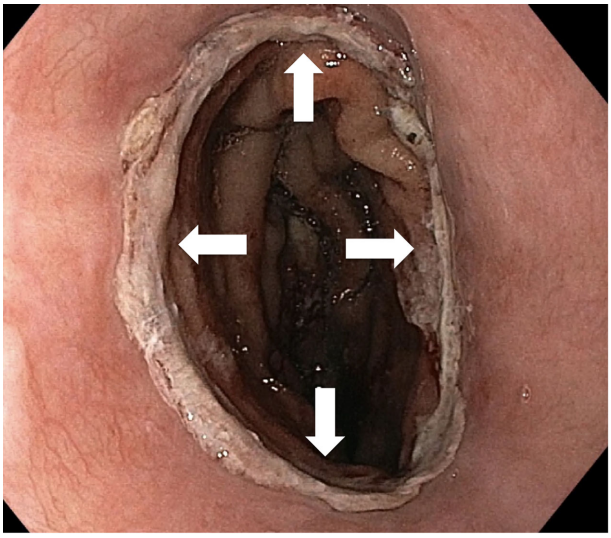

Fig. 1 Uneventful healing of the esophagogastrostomy with granulation tissue (arrows) after 5 days of preemptive endoluminal vacuum therapy.

Statistical analysis

Patient characteristics are expressed as mean (standard deviation) or median (IQR) for continuous variables and frequencies and percentages for categorical variables, respectively.

RESULTS

There were 20 anastomoses at risk in 19 consecutive and unselected patients undergoing MIE between November 2017 and May 2018. One of the ttMIE-patients of this series underwent rethoracotomy and high intrathoracic reanastomosis with pEVT at postoperative day 12 for gastric tube redundancy preventing adequate oral feeding. Patient characteristics are shown in Table 2.

Technical aspects of pEVT

In one patient, proximal dislocation of the device occurred at postoperative day 1. He underwent immediate endoscopic repositioning of the sponge without any further complications. There were no other adverse events related to pEVT. In particular, there were no bleeding episodes, tracheobronchial fistulae, air leaks, or disconnections. In all patients, endoscopic removal of the Eso-SPONGE system was performed routinely 5 (IQR 3–6) days after surgery without complications. Technical-procedural aspects of sponge extraction and anastomotic healing did not differ significantly in patients undergoing early or later removal of the device.

Anastomotic healing

Uneventful primary healing occurred in 19 of 20 anastomoses (Fig. 1) (AL rate 5%, stenosis rate 0%). In one patient after ttMIE, a 2 mm contained AL (ECCG type 2) was detected during endoscopic sponge removal (Fig. 2a). This patient was an american society of anesthesiologists grade III high-risk case with a Charlson comorbidity index of 7 (insulin-dependent diabetes type II, history of myocardial infarction and chronic kidney disease). Throughout the postoperative course, he remained asymptomatic without clinical signs of infection with unremarkable c-reactive protein levels and leukocyte counts. After a second course of EVT over 5 days, the leak was closed (Fig. 2b) and followed by an uneventful clinical course until discharge 20 days after surgery.

Postoperative morbidity (Table 3)

Postoperative intensive care unit and hospital stay was 1 (IQR 1–3) and 13 (IQR 11–18) days, respectively. There were no deaths in this series and none of the patients experienced morbidity > CD IIIb. Seven patients (37%) had no postoperative complication, eight patients (42%) developed one complication, and four patients (21%) experienced two or more complications. The highest morbidity seen in this series was a CD IIIb complication in a patient undergoing revisional surgery at postoperative day 12 for redundancy of the gastric tube with failure of transition to oral diet. Open transthoracic revisional surgery was performed with shortening of the interponate, end-to-side reanastomosis, and pEVD. The anastomotic healing of both the primary and revisional anastomosis was uneventful.

Four patients (21%) had a CD IIIa complication. In detail, one patient developed an ECCG type 2 AL that was managed conservatively (EVT), two patients showed a pleural effusion that was treated with thoracic drainage, and one patient had a pyloric outlet obstruction requiring a single endoscopic dilation. The median CCI 30 days after surgery was 20.9 (IQR 0–26.2).

DISCUSSION

This is the first clinical series to evaluate the effect of intraoperative pEVT on anastomotic healing and

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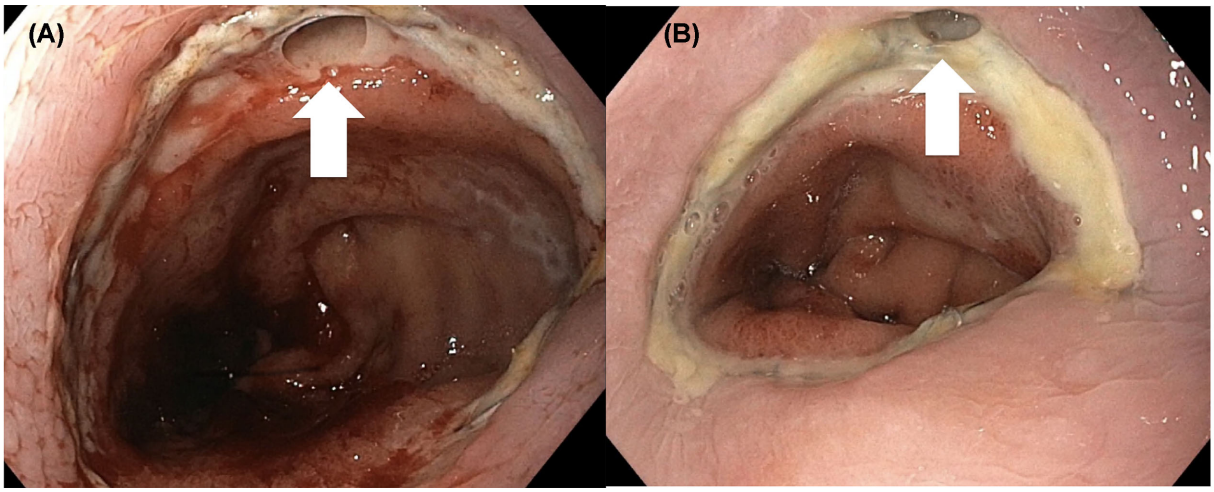

Fig. 2 (A) 2 mm anastomotic leak (arrow) at initial diagnosis on postoperative day 5. (B) The leak (arrow) was sealed and contained after a second stage of endoluminal vacuum therapy over 5 days.

morbidity after esophagectomy. In contrast to other research,[10] the Eso-SPONGE device was placed during surgery, immediately after completion of the anastomosis. The clinical outcome in our study cohort was promising with zero 30-day mortality (5.6% at 90 days) and a single ECCG grade 2 AL (AL rate 5%). Compared with 50 consecutive patients undergoing esophagectomy in our institution before implementation of pEVT, the AL rate in the present series was lower (5% vs 8%) and the clinical course of anastomotic failure was remarkably benign without septic complications.

The mechanism of action of EVT involves increased anastomotic blood flow, modulation of cytokines and chemoreceptor-mediated cell signaling, leading to enhanced angiogenesis and deposition of granulation tissue.[13] In the preemptive setting after esophagectomy (pEVT), this mechanism may help to seal minor unrecognized anastomotic defects at a very early stage, thus preventing contamination of the mediastinum and the pleural space.

In AL after esophagectomy, endoscopic negative pressure therapy has the potential to convert 'free' into 'contained' AL by creating a closed, granulating, and well-drained extraluminal cavity. A contained anastomotic defect is sealed by the surrounding healthy tissue and conservative treatment is successful in 80–100%.[9] To achieve this, the Eso-SPONGE may be positioned intra- or extraluminally, depending on the size of the abscess cavity.[14,15] In our experience, extraluminal (intracavitary) sponge positioning is mainly indicated in larger paraanastomotic caverns with a relevant defect of the suture line. Extraluminal placement may also be combined with a partially covered self-expandable metal stent (stent-over-sponge technique).[9] However, one should keep in mind that positioning of the sponge outside the esophagogastric lumen carries the risk of severe hemorrhage from intrathoracic vessels.[16] Therefore, the benefits of extraluminal Eso-SPONGE placement must be carefully counterbalanced against its potential risks.

The evidence published on pEVT in esophageal surgery is extremely limited. In a pilot study on domestic pigs undergoing Ivor Lewis esophagectomy, [11] intentional anastomotic defects were treated with EVT ($n = 4$) or received no specific treatment (control group, $n = 6$). Three controls died within 24 hours and were excluded from analysis, whereas three controls surviving more than 24 h showed frank AL and pleural contamination with gastric contents. In contrast, no leaks were detected in the EVT group after a follow-up of 3–7 days ($p = 0.03$) and the authors concluded that EVT may have the potential to close leaks that otherwise would not heal without surgical or endoscopic intervention.

A retrospective case-series investigated early postoperative EVT [10] in patients undergoing Ivor Lewis esophagectomy with endoscopically proven anastomotic ischemia. EVT led to complete mucosal recovery without AL in six of eight patients. Two patients developed small, contained ALs that were successfully treated by subsequent courses of EVT. No EVT-related adverse events were noted. The authors concluded that EVT may play an important role in the treatment of anastomotic ischemia following esophagectomy.

Both studies cited above focus on treatment of ischemia or AL, which represents a well-established indication for EVT. In contrast, the idea of our study was to promote primary anastomotic healing in a technically sound surgical situation that carries a high

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Table 3 Postoperative outcomes (20 anastomoses at risk in 19 patients)

Complications, *n* (%)	
Any type	12 (63)
Minor (CD II–IIIa)	7 (58)
Major (CD IIIb–V)	1 (5)
Anastomotic leak*	1 (5)
Conduit necrosis	0 (0)
Chyle leak	0 (0)
Gastrointestinal event	4 (21)
Pulmonary event	5 (26)
Cardiac event	5 (26)
Thromboembolic event	0 (0)
Urologic event	0 (0)
Infection	3 (16)
Neurologic event	3 (16)
Wound infection	0 (0)
Blood product utilization, *n* (%)	
Intraoperative	0 (0)
Postoperative	1 (5)
Intra- and postoperative	1 (5)
ICU stay, median (IQR)	1 (1–3)
Hospital stay, median (IQR)	13 (11–18)
Readmission rate within 90 days of discharge, *n* (%)	
Related to esophagectomy	3 (16)
Unrelated to esophagectomy	0 (0)
CCI at 30 day after discharge, median (IQR)	20.9 (0–26.2)
Mortality, *n* (%)	
30-day	0 (0)
90-day	1 (5.6)

*Twenty anastomoses at risk in 19 patients.
IQR interquartile range; CD, Clavien–Dindo classification; ICU, intensive care unit; CCI, comprehensive complication index.

intrinsic risk for perioperative morbidity. Thus, to our best knowledge, this is the first clinical series investigating a truly preemptive use of EVT after esophagectomy in humans.

Undeniably, our study has some limitations. First, an additional endoscopic procedure to remove the Eso-SPONGE was required in all patients, and the risk of endoscopy-associated complications must be carefully weighed against the potential benefits of pEVT. Furthermore, there are no accepted standards for ideal treatment duration and optimal negative system pressure. Therefore, those parameters had to be chosen empirically from our experience with EVT for anastomotic fistula. However, complete removal of the sponge without residua was unproblematic and the negative pressure of 75 mmHg was sufficient to promote visible formation of granulation tissue.

Proximal dislocation of the device occurred in one patient at postoperative day one. Dislodgement of nasogastric tubes is a well-known problem occurring in up to 62% of patients during the early postoperative phase.[17] In patients at risk, we switched from traditional nasal tape fixation to a specifically designed anchoring device (AMT Bridle, Applied Medical Technology, Brecksville, OH) with no further dislodgements seen in this series. Another concern was that intraluminal placement of the sponge could promote aspiration of saliva. On the other hand, occlusion of the anastomotic area may also have a protective effect for aspiration pneumonia, because the contents of the gastric tube are completely sealed off the supraglottic area. Either way, no signs of aspiration pneumonia were detected in our series. Also, we are not able to report long-term endoscopic follow-up in our patients. Thus, late complications of pEVT like anastomotic strictures may have been missed and should be evaluated in future prospective clinical trials.[18] However, most patients treated in this series had uneventful transition to a normal diet.

In conclusion, preemptive endoluminal vacuum therapy is a safe procedure that may reduce AL formation and related morbidity by promoting primary anastomotic healing. Furthermore, pEVT is likely to seal potential minor full-thickness defects at a very early stage and thereby prevent free leakage in patients undergoing esophagectomy. Preemptive endoluminal vacuum therapy may be particularly valuable in patients with relevant comorbidities and increased risk for AL. Identification of subpopulations that will benefit most from pEVT should be the next step of clinical research in this field.

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