Endoscopic vacuum therapy for anastomotic leak in esophagectomy and total gastrectomy: a systematic review and meta-analysis

Guilherme Tavares,1,* Francisco Tustumi,1,2,3 Luca Schiliró Tristão,1 Wanderley Marques Bernardo1,2
1 Department of Evidence-Based Medicine, Centro Universitário Lusíada, São Paulo, Brazil 2 Department of Evidence-Based Medicine, Universidade de São Paulo, São Paulo, Brazil 3 Department of Surgery, Hospital Israelita Albert Einstein, São Paulo, Brazil

SUMMARY. The curative treatment for esophageal and gastric cancer is primarily surgical resection. One of the main complications related to esophagogastric surgery is the anastomotic leak. This complication is associated with a prolonged length of stay, reduced quality of life, high treatment costs, and an increased mortality rate. The placement of endoluminal stents is the most frequent endoscopic therapy in these cases. However, since its introduction, endoscopic vacuum therapy has been shown to be a promising alternative in the management of this complication. This study primarily aims to evaluate the efficacy and safety of endoscopic vacuum therapy for the treatment of anastomotic leak in esophagectomy and total gastrectomy. A systematic review and meta-analysis was performed. Studies that evaluated the use of endoscopic vacuum therapy for anastomotic leak in esophagectomy and total gastrectomy were included. Twenty-three articles were included. A total of 559 patients were evaluated. Endoscopic vacuum therapy showed a fistulous orifice closure rate of 81.6% (rate: 0.816; 95% CI: 0.777–0.864) and, when compared to the stent, there is a 16% difference in favor of endoscopic vacuum therapy (risk difference [RD]: 0.16; 95% CI: 0.05–0.27). The risk for mortality in the endoscopic vacuum therapy was 10% lower than in endoluminal stent therapy (RD: −0.10; 95% CI: −0.18 to −0.02). Endoscopic vacuum therapy might have a higher rate of fistulous orifice closure and a lower rate of mortality, compared to intraluminal stenting.

KEY WORDS: negative pressure wound therapy, anastomotic leak, esophagectomy, gastrectomy, meta-analysis.

INTRODUCTION

In 2016, the estimated incidence of esophageal and stomach cancer was 1,600,000 cases worldwide.1 In the same year, approximately 1,249,000 deaths occurred due to these neoplasms.1 The curative treatment for esophageal and gastric cancer is primarily surgical resection, that is, esophagectomy and gastrectomy, respectively.2,3

Anastomotic leak is one of the main complications related to esophagogastric surgery.4,5 The incidence of this complication varies between 0% and 30%6,7 and is associated with a prolonged length of stay in the intensive care unit and hospitalization, reduced quality of life, high treatment costs, and an increased mortality rate.7–9

The management of anastomotic leak is often complex. Endoscopic treatments have gained space in attempt to decrease the morbidity of the leak. The placement of endoluminal self-expandable metal stent (SEMS) is the most frequent endoscopic therapy in these cases. However, since its introduction, endoscopic vacuum therapy (EVT) has been shown to be a promising alternative in the management of this complication.10 This involves the transoral introduction into the esophageal lumen of a porous polyurethane sponge, connected to a drainage tube that generates continuous negative pressure, facilitating the drainage of the cavity, control of edema and stimulation of scar tissue, favoring the closure of the leak.11

This study primarily aims to evaluate the efficacy and safety of EVT for the treatment of anastomotic leak in esophagectomy and total gastrectomy. The secondary aim is to compare EVT and SEMS for the treatment of this complication, providing the best evidence currently available.

METHODS

This systematic review was submitted to the International Prospective Register of Systematic Reviews (PROSPERO)12 under trial registry CRD42020154192.

The search for evidence was carried out independently by two researchers in the following virtual scientific information bases: Medline (PubMed),
The quality of the evidence was graded as high, the assessment tool for cohort-type studies, Robins-stay, complications, and mortality. The closure rate, treatment duration, length of hospital stay, complications, and mortality were evaluated, 395 of whom underwent vacuum therapy and meta-analyzed using RevMan 5.4 software and standard deviation. In categorical measures, the results were mean difference and standard deviation. In categorical measures, the results were risk difference and number necessary to treat or to harm, considering the number of patients. The heterogeneity of effect sizes among studies was assessed with the I² statistic. A random effects model was performed. Pooled-effect measures were calculated with 95% confidence intervals (CI). Funnel plot was used to investigate risk of publication bias. The significance level used was 0.05.

RESULTS

As shown in Fig. 1, 157 articles were retrieved in the Medline (PubMed) database and 514 articles in the EMBASE, Central (Cochrane), and Lilacs (BVS) databases. Excluding duplicates (91 studies), 580 articles remained to be selected. One hundred and three articles were assessed for the risk of bias using the assessment tool for cohort-type studies, Robins-I. The quality of the evidence was graded as high, moderate, low, or very low by the GRADE tool. The comparative studies included were aggregated and meta-analyzed using RevMan 5.4 software and the noncomparative ones were meta-analyzed using Comprehensive Meta-Analysis 3. The measures used to express benefit and harm varied according to the outcomes and were expressed by continuous variables (mean and standard deviation) or by categorical variables (absolute number of events). In continuous measures, the results were mean difference and standard deviation. In categorical measures, the results were risk difference and number necessary to treat or to harm, considering the number of patients. The heterogeneity of effect sizes among studies was assessed with the I² statistic. A random effects model was performed. Pooled-effect measures were calculated with 95% confidence intervals (CI). Funnel plot was used to investigate risk of publication bias. The significance level used was 0.05.

NONCOMPARATIVE STUDIES

Fistulous orifice closure rate

Twenty-one studies analyzed this outcome. Five hundred and twenty-two patients that underwent EVT were evaluated. See Table 1 and Figures 2–4.

The analysis of all cases (esophagectomy and total gastrectomy) showed a closure rate of the fistulous orifice of 81.6% (rate: 0.816; 95% CI: 0.757–0.864; certainty of evidence: very low). When only esophagectomy was included, 14 articles performed this analysis including 248 patients and the observed closure rate was 79.5% (rate: 0.795; 95% CI: 0.711–0.860; certainty of evidence: very low). When only total gastrectomy was included, four studies evaluated the closure rate, including 138 patients, and a rate of 90% was observed (rate: 0.90; 95% CI: 0.749–0.965; certainty of evidence: very low).

Stenosis

Sixteen studies analyzed this outcome. Four hundred and thirty-one patients that underwent EVT were evaluated. See Table 1 and Figures 5–7.

The analysis of all cases (esophagectomy and total gastrectomy) showed a stenosis rate of 12.5% (rate: 0.125; 95% CI: 0.086–0.180; certainty of evidence: very low). When only esophagectomy was included, nine articles performed this analysis, including 161 patients and a stenosis rate of 15.9% was observed (rate: 0.159; 95% CI: 0.088–0.270; certainty of evidence: very low). When only total gastrectomy was included, four studies evaluated the rate of stenosis, including 138 patients, and showed a rate of 9.2% (rate: 0.092; 95% CI: 0.030–0.252; certainty of evidence: very low).

COMPARATIVE STUDIES

Fistulous orifice closure rate

Five studies analyzed this outcome. Two hundred and twenty-six patients were evaluated, and 164 underwent endoluminal stent placement. The pressures used in vacuum therapy were: 20, 50, 70, 80, 100, 125, and 175 mm Hg. The baseline characteristics of the included studies are mentioned in Supplementary File 1.

Quantitative analysis was performed using comparative (vacuum therapy vs. endoluminal stent) and noncomparative studies. The summary of the risk of bias is in Supplementary File 2 and full assessment is in Supplementary File 3, and the certainty of the evidence is in the Supplementary File 4.

CONCLUSION

The pressure used in vacuum therapy was 20, 50, 70, 80, 100, 125, and 175 mm Hg. The baseline characteristics of the included studies are mentioned in Supplementary File 1.

Quantitative analysis was performed using comparative (vacuum therapy vs. endoluminal stent) and noncomparative studies. The summary of the risk of bias is in Supplementary File 2 and full assessment is in Supplementary File 3, and the certainty of the evidence is in the Supplementary File 4.
The analysis of all cases (esophagectomy and total gastrectomy) showed a difference of 16% favoring vacuum therapy (risk difference [RD]: 0.16; 95% CI: 0.05–0.27; \( P = 0.006; I^2: 25\%\); certainty of evidence: moderate). When considering only esophagectomy,\(^{33,35}\) there was superiority of vacuum therapy over the endoluminal stent (RD: 0.26; 95% CI: 0.08–0.45; \( P = 0.005; I^2: 0\%\); certainty of evidence: very low). Only one study\(^{20}\) evaluated the fistulous orifice closure rate for total gastrectomy, showing no statistically significant difference between the groups (RD: 0.07; 95% CI: −0.08 to 0.22; \( P = 0.36\); certainty of evidence: moderate).

**Treatment duration**

Five studies\(^{20,22,29,33,35}\) analyzed this outcome. Two hundred and twenty-six patients were evaluated, 74 of whom underwent vacuum therapy and 152 underwent endoluminal stent placement. There was no difference between the groups, both for esophagectomy and total gastrectomy. See Table 1 and Figure 9.
### Table 1: Summary of the results (noncomparative and comparative studies)

<table>
<thead>
<tr>
<th>Results</th>
<th>Noncomparative studies</th>
<th>Comparative studies (SEMS × EVT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Closure rate</td>
<td>Stenosis</td>
</tr>
<tr>
<td>Esophagectomy + total</td>
<td>6%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>(Rate: 0.816; CI 0.777–0.864)</td>
<td>(Rate: 0.125; CI 0.086–0.180)</td>
</tr>
<tr>
<td>Esophagectomy</td>
<td>79.5%</td>
<td>15.9%</td>
</tr>
<tr>
<td></td>
<td>(Rate: 0.795; CI 0.711–0.860)</td>
<td>(Rate: 0.159; CI 0.088–0.270)</td>
</tr>
<tr>
<td>Total Gastrectomy</td>
<td>90%</td>
<td>9.2%</td>
</tr>
<tr>
<td></td>
<td>(Rate: 0.90; CI 0.749–0.965)</td>
<td>(Rate: 0.092; CI 0.038–0.252)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; EVT, endoscopic vacuum therapy; MD, mean difference; RD, risk difference; SEMS, endoluminal self-expandable metal stent.

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**Fig. 2** Fistulous orifice closure rate. Noncomparative analysis, evaluating endoscopic vacuum therapy, including both surgeries, esophagectomy, and total gastrectomy.

**Hospital stay**

Five studies analyzed this outcome. Two hundred and sixteen patients were evaluated, 80 of whom underwent vacuum therapy and 136 underwent endoluminal stent placement. There was no difference between the groups, both for esophagectomy and total gastrectomy. See Table 1 and Figure 10.
Complications
Five studies20,22,29,33,35 analyzed this outcome. Two hundred and twenty-six patients were evaluated, 74 of whom underwent vacuum therapy and 152 underwent endoluminal stent placement. There was no difference between the groups, both for esophagectomy and total gastrectomy. See Table 1 and Figure 11.

Mortality
Six studies20,22,29,33,35,36 analyzed this outcome. Two hundred and fifty-five patients were evaluated, 91 of whom underwent vacuum therapy and 164 underwent endoluminal stent placement. See Table 1 and Figure 12.

The analysis of all cases (esophagectomy and total gastrectomy) showed that vacuum therapy was associated with a lower risk for mortality (RD: −0.10; 95% CI: −0.18 to −0.02; $P = 0.01$; $I^2$: 0%; certainty of evidence: moderate). When considering only esophagectomy,33,35,36 there was superiority of vacuum therapy over endoluminal stent (RD: −0.22; 95% CI: −0.37 to −0.06; $P = 0.006$; $I^2$: 0%; certainty of evidence: low). Only one study20 evaluated mortality for total gastrectomy, showing no statistically significant difference between the groups (RD: −0.04; 95% CI: −0.17 to 0.10; $P = 0.61$; certainty of evidence: moderate).
DISCUSSION

This article demonstrated that EVT has a high rate of closure of the fistulous orifice, with a rate of 80% for esophagectomy and 90% for total gastrectomy with esophagojejuno-anastomosis. When compared to the endoluminal stent, EVT seems to be more likely to close the fistulous orifice and shown less mortality, considering esophagectomy and total gastrectomy together. Besides that, EVT apparently has a higher fistulous orifice closure rate and less mortality, considering esophagectomy.

Vacuum therapy promotes healing of the leak through several mechanisms of action. The vacuum therapy results in increased microvessel density through the generation of temporary hypoperfusion at the edges of the leak, leading to increased angiogenesis. This mechanism is particularly important in esophagectomy, in which the anastomosis perfusion is the Achilles’ heel for leakage.
Vacuum therapy also acts by other mechanisms. The accumulation of fluid in the extracellular space and tissue edema inhibit healing by compressing local cells and tissues. Therefore, by removing fluid, vacuum therapy reduces the compression forces that act on the microvasculature, allowing an increase in blood flow and tissue perfusion, improving healing.\(^{43,47,48}\) Furthermore, it is known that a high bacterial load can interfere with the healing process of the fistula; however, the evidence is conflicting about the role of vacuum therapy in reducing bacterial contamination.\(^{43}\) However, vacuum therapy will not work on surgical technical imperfections, such as anastomotic tension or torsion, and probably in these conditions, EVT will have low effectiveness.

However, for the best management of anastomotic leakage, it is important to know and correct all the underlying conditions that may have contributed to the leak. Malnutrition, hemodynamic instability, and diabetes are among the risk factors and need to be compensated for higher chance of anastomotic closure.\(^{49-51}\) Certain risk factors for leakage, however, cannot be modified, such as age, and previous history of heart failure, coronary heart disease, and vascular disease.\(^{49-51}\)
This study has limitations. The articles included are all observational cohorts and case series. Therefore, these study designs have low level of evidence. In addition, they have a small sample size, a variety of surgical techniques, as well as different pressures used in EVT. It is well known that there is a high heterogeneity between the Ivor Lewis and McKeown techniques, with the Ivor Lewis technique being associated with lower postoperative morbidity due to significantly reduced leakage rates through the fistula, fewer pulmonary complications, stenosis, dysphagia, and recurrent laryngeal nerve palsy, compared to McKeown’s surgical technique.\(^\text{52–55}\) The major risk of bias probably is regarding how patients were selected to either vacuum therapy or stent. Since EVT use has increased in the last years, maybe patients could be more prone to get vacuum therapy and a shorter stay related to Enhanced Recovery After Surgery Society recommendations.\(^\text{56}\) Thus, randomized clinical trials are required, with greater standardization between operations, as well as the pressures used in EVT.

**CONCLUSION**

EVT is effective and has a high rate of closure of the fistulous orifice. Besides that, EVT seems to have better safety than the endoscopic stent for the treatment of anastomotic leak in esophagectomy and total gastrectomy. Future randomized trials comparing EVT with endoluminal stent are needed to confirm these findings.
Fig. 11 Complications. Analysis comparing endoscopic vacuum therapy with endoluminal stent. Legend: performing the meta-analysis, esophagectomy, and gastrectomy were considered as a subgroup due to the impossibility of separating these data in the respective studies.

SUPPLEMENTARY DATA

Supplementary data mentioned in the text are available to subscribers in DOTESO online.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.
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References


