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Review

Endoscopic vacuum therapy versus endoscopic stenting for upper gastrointestinal transmural defects: Systematic review and meta-analysis

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Background: Upper gastrointestinal fistulas, leaks, and perforations represent a high cost burden to health systems worldwide, with high morbidity and mortality rates for affected patients. Management of these transmural defects remains therapeutically challenging.

Objectives: The aim of this study is to perform a systematic review and meta-analysis to investigate the efficacy and safety of self-expanding metal stents (SEMS) versus endoscopic vacuum therapy (EVT) for treatment of upper gastrointestinal transmural defects.

Methods: Searches were performed on MEDLINE, EMBASE, Central Cochrane, Latin American and Caribbean Health (LILACS), and gray literature, as well as a manual search to identify studies comparing SEMS versus EVT to treat upper gastrointestinal transmural defects. Evaluated outcomes were: rates of successful closure, mortality, length of hospital stay, duration of treatment, and adverse events.

Results: Five studies with a total of 274 patients were included. There was a 21% increase in successful fistula closure attributed to EVT compared with the SEMS group (RD 0.21, CI 0.10–0.32; $P = 0.0003$). EVT demonstrated a 12% reduction in mortality compared to stenting (RD 0.12, CI 0.03–0.21; $P = 0.006$) and an average reduction of 14.22 days in duration of treatment (CI 8.38–20.07; $P < 0.00001$). There was a 24% reduction in adverse events (RD 0.24, CI 0.13–0.35; $P = 0.0001$. There were no statistical differences between the studied therapies regarding the length of hospital stay.

Conclusion: Endoscopic vacuum therapy proves to be superior in successful defect closure, mortality, adverse events and duration of treatment.

Key words: EVT, endoscopic vacuum therapy, stent, leak, fistula

INTRODUCTION

GASTROINTESTINAL TRANSMURAL DEFECTS can be classified into three distinct entities – fistulas, leaks and perforations.[1] They represent a therapeutic challenge that directly impacts mortality, morbidity, and patients' quality of life, in addition to increasing costs to health systems around the world.[2–5] It is important to recognize that there are many etiologies and presentations, and many treatment approaches, depending on patient status and whether the surrounding tissue is otherwise healthy.[1]

In recent years, endoscopic treatment has come to the forefront as first-line therapy.[2,6] Among the available treatment modalities, self-expanding metal stents (SEMS) have been validated as an effective option in the current literature in various gastrointestinal urgencies and emergencies.[2,7–13] Nevertheless, complications associated with stents are highly variable, including low and high rates of migration, bleeding and stenosis.[3,14]

Preliminary studies have shown that use of endoscopic vacuum therapy (EVT) is associated with improved rates of successful defect closure, lower rates of adverse events, and

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lower mortality compared to surgical strategies and even when compared to endoscopic approaches employing stents.[15–17]

Thus, the aim of this study is to compare the efficacy and safety of EVT versus SEMS for the treatment of upper gastrointestinal transmural defects.

MATERIALS AND METHODS

Protocol and registration

THIS SYSTEMATIC REVIEW was designed according to the Cochrane Handbook of Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) handbook Cochrane;[18] The study was registered in the International Prospective Register of Systematic Reviews (PROSPERO)[19] – available in https://www.crd.york.ac.uk/prospero, maintained by the Centre for Reviews and Dissemination, University of York (England), under the code CRD42019137737. Following the commencement of the study, there were no amendments and no deviations from the protocol. The study was approved by the Research Ethics Committee of the University of São Paulo School of Medicine Hospital das Clínicas and written consent was not required as this was a systematic review project.

Eligibility criteria

Types of studies. Cohorts comparing EVT versus SEMS for treatment of upper gastrointestinal transmural defects. Exclusion criteria were: non-comparative studies, non-explicit study design, studies with insufficient data, and studies without full text provided.

Types of participants. Patients diagnosed with upper gastrointestinal transmural defects (fistulas, leaks, or perforations) of any etiology, including inadvertent postoperative defects status-post esophagectomy, gastrectomy, esophageal fundoplication, and diverticulectomy, and those with idiopathic Boerhaave syndrome.

Types of interventions. Both EVT and SEMS used for the treatment of upper gastrointestinal transmural defects.

Additional interventions. Berlth *et al.*[15] performed endoscopic placement of double-lumen nasogastric feeding tube or a triple-lumen diverted nasogastric feeding tube, intravenous antimicrobials (including antifungals). In the event of mediastinal, pleural, or abdominal fluid collection, external drainage of the leaks was interventionally applied, either ultrasonically guided or CT-guided. Hwang *et al.*[16] changed the treatment course to surgery in three patients. Mennigen *et al.*[17] managed small residual fistulas persisting after stent removal by OTSC placement in one patient and application of fibrin glue in one patient. Brangewitz *et al.*[20] performed endoscopic clips in five patients before stent application. Four of these patients received additional fibrin glue injection. One patient, with additional bronchoesophageal fistula, used a septum occluder.

Outcomes. The primary outcomes assessed were mortality and successful rate of defect closure. The definition of successful closure was variable between studies, which makes comparability limited. Most studies did not define time for closure. Although there was no information regarding chronicity, the assessed cases are about acute diseases. Berlth *et al.*[15] defined success as the state in which the endoscopy confirmed complete healing and the patient no longer had any clinical signs of a persistent leak. Mennigen *et al.*[17] defined success as anastomotic healing as proven by endoscopy and x-ray contrast study, and patient recovery. Brangewitz *et al.*[20] defined successful closure if radiological or endoscopic imaging showed successful closure and if the patient had no clinical signs of persistent leakage, could be discharged from the hospital and had no signs of leakage recurrence in the follow-up. Lastly, Hwang *et al.*[16] defined clinical success in the E-SEMS group as complete healing of the perforation or leakage by the placement of single or multiple stents irrespective of whether the stent was left in situ or was removed. In the EVT group success was defined as complete healing of the perforation or leakage by EVT irrespective of whether multiple endoscopic vacuum therapies were utilized. Secondary outcomes were adverse events, length of hospital stay, and duration of treatment. The definition of adverse events was graded according to the American Society for Gastrointestinal Endoscopy (ASGE) lexicon as mild, moderate, severe and fatal.[21]

Information sources and search

Individualized search strategies for Medline, Embase, Cochrane Central Register of Controlled Trials, and LILACS were performed from inception through June 2020. A manual search and gray literature search was also conducted by reviewing all references regarding the topic. The search strategy employed was the same in all databases, namely: (leak OR leakage OR sleeve OR surgery OR postoperative complications OR transmural OR fistula OR perforation) AND (negative pressure OR vacuum OR EVT

OR evac OR SEMS) AND (endoscopy OR endoscopic OR endoluminal).

Study selection and data collection process

All relevant articles irrespective of year of publication, type of publication, or publication status were included. Titles and abstracts of all potentially relevant studies were screened for eligibility. Duplicates were removed. Two reviewers (ESSJ and IBR) independently screened titles and abstracts of all the articles according to predefined inclusion and exclusion criteria. Any differences were resolved by mutual agreement and in consultation with the third reviewer (EGHM). The researchers used Excel sheets to extract relevant data and results.

Data extraction

After selecting the studies for final analysis, the following data were collected: authors, country, publication year, study type, the total number of included patients (with baseline patient characteristics, as available), etiology of the upper gastrointestinal transmural defect, neoadjuvant therapy, prosthesis characteristics, negative pressure regimen, vacuum system and the number of endoscopies and sponges required. Measured outcomes extracted from the studies were: rates of successful defect closure, duration of therapy (both time for the diagnosis to the beginning of treatment, and time from beginning to the end of treatment), in-hospital mortality, time in ICU, hospitalization and adverse events.

Summary measures and synthesis of results

We used the software RevMan 5 (Review Manager version 5.3.5 – Cochrane Collaboration, Oxford, United Kingdom) to carry out the data analysis, generate forest plots, and calculate confidence intervals. Absolute values, means, and standard deviations were used in the data analysis. For studies that did not report mean and standard deviation, data standardization was estimated using mathematical formulae.[22]

Regarding dichotomous variables, we calculated the risk difference using the Mantel-Haenszel method. Mean difference (MD) was used for continuous variables, being determined by inverse variance. The confidence interval (CI) of 95% was established for both measures. Heterogeneity was calculated by means of the Higgins method (I^2) and Chi-Squared test (X^2). Values of heterogeneity obtained in each analysis defined the application of either fixed (value < 50%) or random-effects (value > 50%) models.

Risk of bias in individual studies

The risk of bias in the studies was assessed by means of Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I). We performed a full analysis of each outcome in all included studies. To simplify the analysis, we evaluated the global risk of bias in each study, using the same domains suggested in ROBINS-I.

Risk of bias across studies and quality of evidence (GRADE)

We assessed the selected cohorts using the ROBINS-I tool. Seven different domains are taken into account. The risk of bias for each specific domain is assessed as "low risk of bias," "moderate risk of bias," "serious risk of bias," "critical risk of bias," and "no information" for each outcome, according to criteria described in detail on the Cochrane Handbook.[23]

The quality of evidence was assessed using the objective criteria of GRADE (Grading of Recommendations Assessment, Development and Evaluation) for each outcome and resulted by means of GRADEpro – Guideline Development Tool software (McMaster University, 2015; Evidence Prime, Inc., Hamilton, Ontario, Canada). The items considered for assessment are: study design, evaluation of the risk of bias, inconsistency, indirect evidence, imprecision, and publication bias. The assessment of the risk of bias and quality of the studies was performed under the supervision of our statistical analysis team.

RESULTS

Study selection

A TOTAL OF 6170 studies were identified by means of initial search criteria. After removing duplicated entries, 4110 studies were considered. Of these, 163 remained after abstract evaluation. After applying exclusion criteria, 28 studies were eligible for full-text assessment, of which 23 were excluded (case series, case reports, and non-systematic reviews). Therefore, five studies were selected for qualitative synthesis and meta-analysis (Fig. 1).

Study characteristics

Five studies were included in this meta-analysis,[15–17,20,24] four from Germany and one from South-Korea. A total of 274 patients were included; 105 patients in the EVT group and 169 in the SEMS group. The characteristics of the studies are demonstrated in Figure 2. The individual characteristics of the patients per study are shown in Table 1.

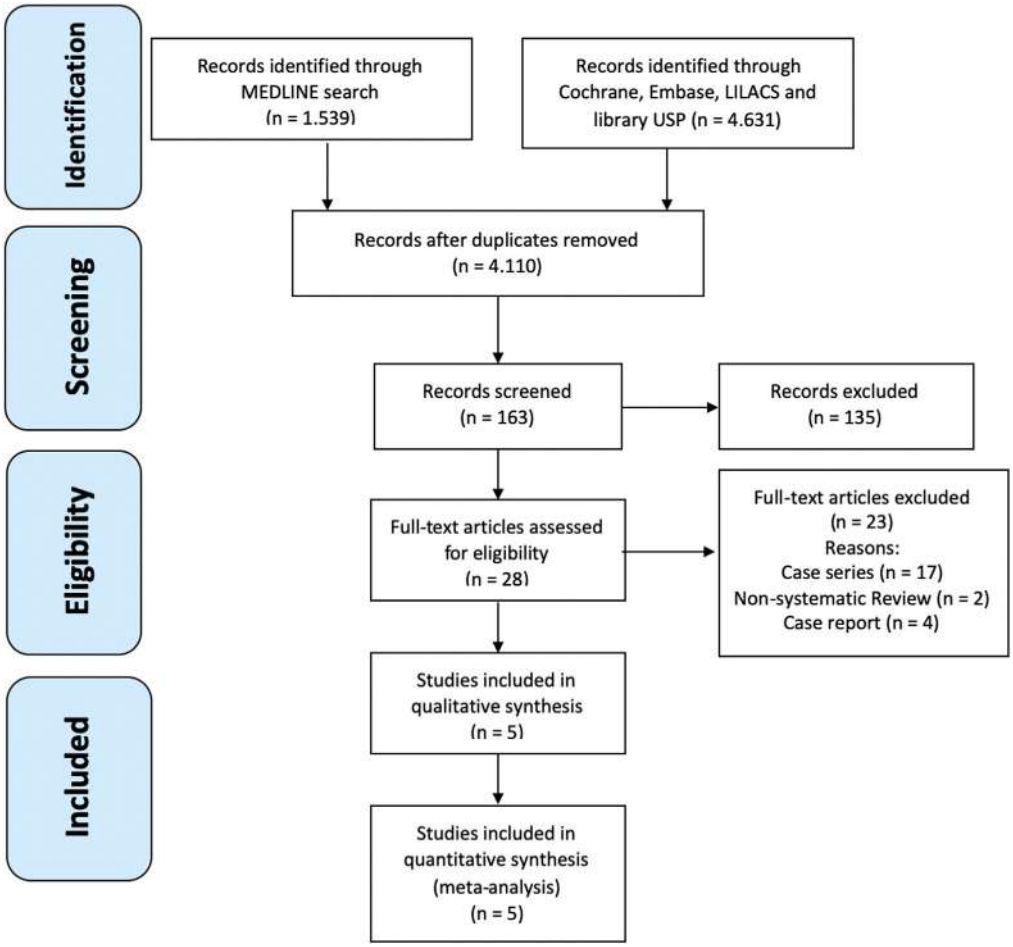

Figure 1 Flow diagram showing study selection process for meta-analysis.

- Berlth *et al.*[15]: The authors assessed 111 patients diagnosed with postoperative fistulas or leaks in either esophagojejunal or esophagogastric anastomoses. All 111 surgical operations were performed with curative intent for malignancy. Successful closure, mortality, duration of treatment, length of hospital stay, and adverse events were compared for patients treated with EVT (n = 34) versus SEMS (n = 77).
- Hwang *et al.*[16]: A South-Korean study conducted in Seoul from 2008 to 2014. The authors assessed 18 patients diagnosed with postoperative leaks in esophagogastric anastomoses status-post esophagectomy (Mckeown or Ivor-Lewis) or gastrectomy for malignant indications. Successful closure, mortality, duration of treatment, and adverse events were compared for patients treated with EVT (n = 7) versus SEMS (n = 11).
- Mennigen *et al.*[17]: The authors assessed 45 patients diagnosed with postoperative defects following abdominothoracic esophagectomy. Successful closure, mortality, duration of treatment, length of hospital stay, and adverse events were compared for patients treated with EVT (n = 15) versus SEMS (n = 30).
- Schniewind *et al.*[24]: The authors assessed 47 patients diagnosed with postoperative leaks in esophagogastric anastomoses status-post esophagectomy (Mckeown or Ivor-Lewis). Mortality and length of hospital stay were compared for patients treated with EVT (n = 12) versus SEMS (n = 17).
- Brangewitz *et al.*[20]: A German study conducted in Hannover from 2000 to 2011. The authors assessed 71 patients with fistulas, leaks, or perforations after esophagectomies, fundoplications, esophageal

Author	Publication year	Country	Study type	Patients (n)	Stent	EVT	Negative pressure (mm Hg)	Age range stent (mean + – SD)	Age range EVT (mean + – SD	Primary outcome
Berlth et al	2018	Germany	Cohort	111	77	34	125	64 + – 7.5	65 + – 10.2	Successful closure
Hwang et al	2016	South Korea	Cohort	18	11	7	125	67.6 + – 7.5	70.8 + – 4.3	Successful closure
Mennigen et al	2015	Germany	Cohort	45	30	15	100 - 125	65.5 + – 13	57.5 + – 9.8	Successful closure
Brangewitz et al	2013	Germany	Cohort	71	39	32	125	62 + – 11.5	63 + – 9.7	Successful closure
Schniewind et al	2013	Germany	Cohort	29	12	17	70 - 80	NR*	NR*	Successful closure

*NR: not related
EVT: endoscopic vacuum therapy

Figure 2 Characteristics of included studies.

diverticulotomies, Boerhaave syndrome, and iatrogenic perforations. Successful closure, hospitalization, mortality and stricture development were compared for patients treated with EVT (n = 32) versus stent placement (n = 39).

Risk of bias in the included studies

The risk of bias for each study was assessed by ROBINS-I. There was a high risk of bias for all assessed outcomes, which is primarily attributed to the fact that no randomized control trials were included in this study, as there have been none performed in the literature. Thus, the absence of standardization and methodological rigor in the included studies resulted in the risks of bias (Fig. 3).

Rate of successful defect closure

Four of the five studies[15–17,20] reported rate of successful closure as the primary outcome in their analyses. EVT therapy was used in 88 of the 245 patients included in these studies, while SEMS was used in the remaining 157 patients. EVT therapy was shown to increase the rate of successful closure to 21% (RD 0.21, CI 0.10–0.32; P = 0.0003) (Fig. 4). The number needed to treat was 4.76.

Mortality

All five studies[15–17,20,24] assessed patient mortality. EVT therapy was used in 105 patients while SEMS were used in 169 patients. The use of EVT was associated with a 12% reduction in mortality (RD −0.12, CI −0.21–0.03; P = 0.006) (Fig. 5). The needed number to treat was 8.3. The certainty of the evidence for this outcome is very low.

Treatment duration

Four of the five studies[15–17,20] reported treatment duration and were included in this analysis. EVT was performed in 88 patients and SEMS were placed in 157 patients. In patients whom underwent EVT, there was a 14.2% reduction in the average duration of treatment when compared to stenting (Fig. 6).

Length of hospital stay

Four of the five studies[15,17,20,24] assessed the length of hospital stay (reported in days. There was no significant statistical difference observed when comparing the two treatment methods herein studied (MD −4.61, CI −12.80–3.59; P = 0.27) (Fig. 7).

Adverse events

Four studies[15–17,20] assessed the occurrence of adverse events. Adverse events directly related to the intervention were included. EVT was performed in 88 patients and SEMS were placed in 157 patients. In patients who underwent EVT, there was a 24% reduction in adverse events (RD 0.24, CI 0.13–0.35; P = 0.0001) (Fig. 8).

Certainty of evidence

The certainty of the evidence for each outcome was evaluated using the tool GRADEpro. As aforementioned, all cases presented a “very low” certainty of evidence (Table S1).

Table 1 Characteristics of patients per study

Study, treatment method, *n* (%)	Female, *n* (%)	Age, mean and SD, years	Negative pressure (mm Hg)	Oncologic resection %	Neoadjuvant therapy %	Etiology: surgical anastomotic leak %	(Sub-) total esophagectomy %	Reconstruction type esophagogastrostomy %	Cervical leakage, *n* (%)	BMI, mean and SD
Brangewitz *et al.*										
EVT – 32 (45)	4 (13)	63 ± 9.7	125	88	56	94	NR	44	NR	25.2 ± 7.9
SEMS – 39 (55)	9 (23)	62 ± 11.5	NA	74	15	79	NR	69	NR	26.4 ± 3.85
Schniewind *et al.*										
EVT – 17 (59)	NR	NR	70–80	NR	NR	100	100	NR	3 (18)	NR
SEMS – 12 (41)	NR	NR	NA	NR	NR	100	100	NR	1 (8)	NR
Mennigen *et al.*										
EVT – 15 (33)	1 (7)	57.5 ± 9.8	100–125	100	73	100	100	100	0 (0)	NR
SEMS – 30 (67)	9 (30)	65.5 ± 13	NA	93	43	100	100	100	0 (0)	NR
Hwang *et al.*										
EVT – 7 (38)	2 (29)	70.8 ± 4.3	125	100	NR	100	71	NR	0 (0)	NR
SEMS – 11 (61)	2 (18)	67.6 ± 7.5	NA	100	NR	100	36	NR	1 (9)	NR
Berlth *et al.*										
EVT – 34 (30)	5 (15)	65 ± 10.2	125	100	53	100	74	74	0 (0)	NR
SEMS – 77 (70)	14 (18)	64 ± 7.5	NA	100	65	100	88	88	1 (1)	NR

BMI, body mass index; EVT, Endoscopic vacuum therapy; NA, not applicable; NR, not report (No data); SD, Standard deviation; SEMS, Safety of self-expanding metal stents.

DISCUSSION

GASTROINTESTINAL TRANSMURAL DEFECTS can be classified into three distinct entities – fistulas, leaks and perforations.[1] While several treatment modalities are available, including both surgical and endoscopic approaches, the results of the success and safety of these modalities are conflicting, and physicians are consistently searching for safer and more effective strategies.[25–27]

The usage of stents for upper gastrointestinal transmural defects has already been validated in the literature.[3] Self-expandable metal and plastic stents can both be used, although metal stents are the more commonly applied device. However, SEMS can be associated with several adverse events, including patient intolerance and stent migration, which occurs in approximately 20.8% of cases.[28] The risk of migration can be decreased via fixation of the proximal flange of the stent, either via endoscopic suturing devices, cap-mounted over the scope clips, or the nasal bridle technique, however this can add to the procedure duration. Other stent-related complications, such as bleeding and perforation, can occur but are rare (2%).[28,29] Thus, given these potential complications, and only intermediate rates of successful closure, physicians again consider novel-use of alternative therapy for defect closure, including EVT.[14,30]

Endoscopic vacuum therapy allows internal drainage, thus controlling the infection and promoting tissue healing, by deploying a system of polyurethane sponges connected to vacuum pumps, which allows for application of negative pressure to the system.[31] EVT is frequently used for gastroesophageal leaks with clinical success higher than 80%, however, one downside which limits more widespread use is that the sponge system must be exchanged endoscopically every 4–5 days.[28,32,33] Thus, the most important drawback of EVAC is the necessity of performing repeated endoscopic procedures.[20] Novel devices allow exchange once a week, but more studies are necessary to assess the safety and effectiveness.[34,35]

In terms of the rates of successful closure, four of the five studies reported this as an outcome in their study and were thus able to be included in our analysis. We found a risk difference of 21%, which argues towards the superiority of EVT versus SEMS for this outcome, and is in agreement with prior literature which demonstrate a significant increase in success rates noted with EVT.[17,36] However, Berlth *et al.*[15] showed no significant statistics in the analysis. Rates of mortality were lower in the group treated with endoscopic vacuum therapy, despite the fact that this outcome is especially influenced by other variables, from quality of care to intrinsic patient characteristics.[37,38] The study by Hwang

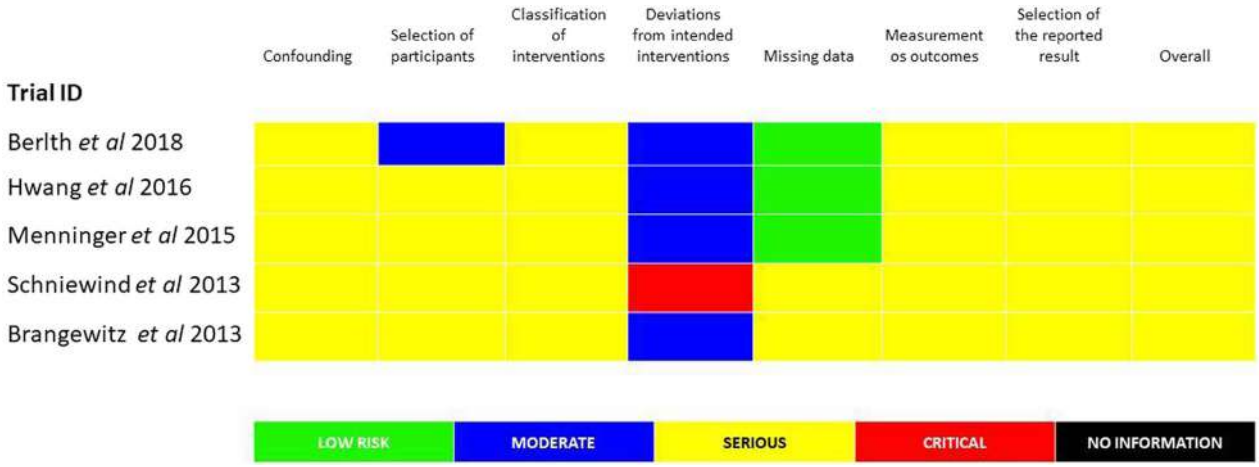

Figure 3 Risk of bias categorized by outcome of individual studies assessed by the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool.

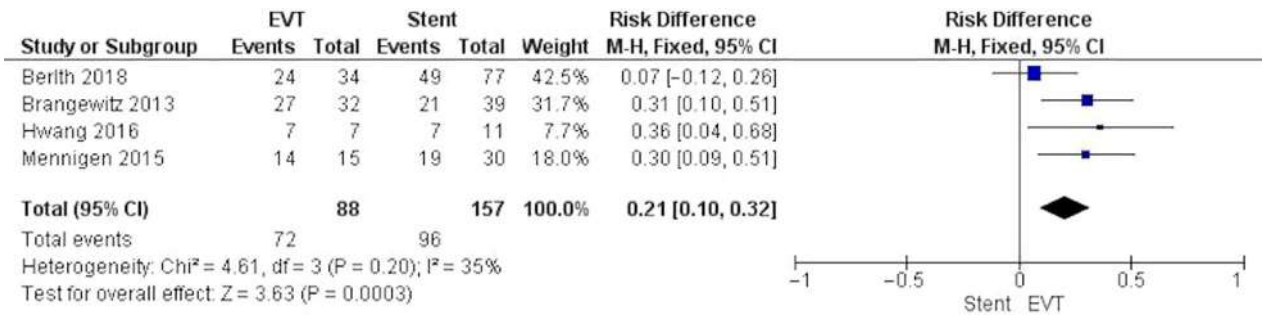

Figure 4 Forest plot for rate of successful closure, using the fixed-effects model, with the Mantel-Haenszel method. CI, confidence interval.

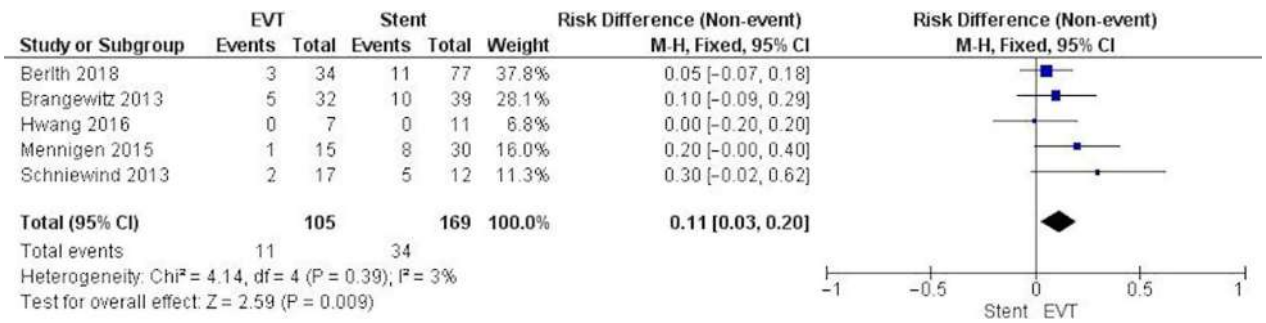

Figure 5 Forest plot for mortality, using the fixed-effects model, with the Mantel-Haenszel method. CI, confidence interval.

et al.[16] reported no mortality in their included patients, but it is worth noting that their study involved the smallest population in our review, and two patients did pass away during follow-up, but the authors attributed this to the underlying disease process rather than the EVT. While there was a reduction in duration of treatment in the EVT versus SEMS group (by 14.22%), the length of hospital stay was not statistically different between the groups. We attribute this apparent paradoxical finding to the patient heterogeneity, lack of standardized care across groups, and potential institutional policies which could be contributing and hinder our analysis.

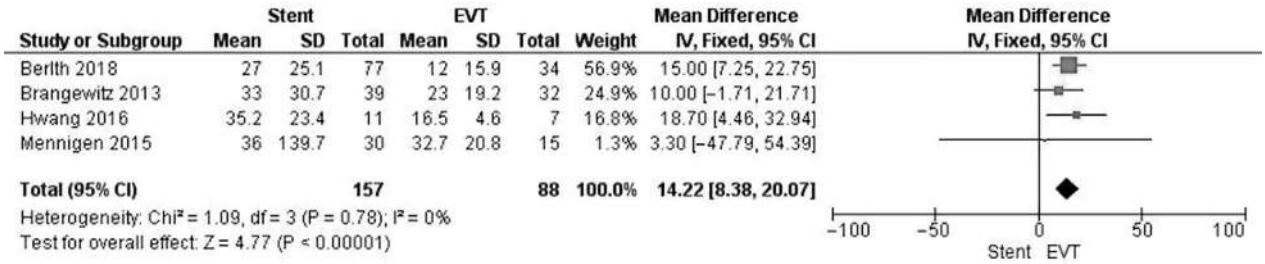

Figure 6 Forest plot for treatment duration using the fixed-effects model, with the Mantel-Haenszel method. CI, confidence interval.

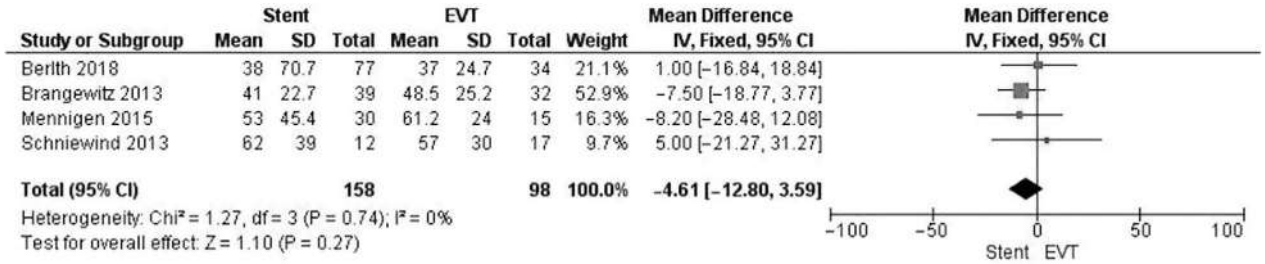

Figure 7 Forest plot for length of hospital stay, using the fixed-effects model, with the Mantel-Haenszel method. CI, confidence interval.

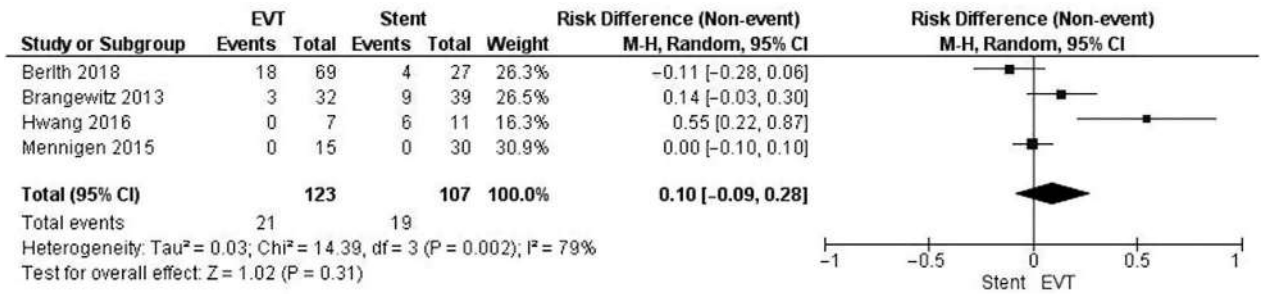

Figure 8 Forest plot for adverse events, using fixed-effects, with the Mantel-Haenszel method. CI, confidence interval.

The size of the leak was different between the manuscripts. Berlth *et al.*[15] reported the size of the leak ranged from one quarter (n = 63, 81.8%), one third (n = 10, 13%) up to one half (n = 2, 2.6%) of the circumference of the esophagus and no description (n = 2, 2.6%) in the SEMS group and from one quarter (n = 22, 64.7%), one third (n = 2, 5.9%), one half (n = 5, 14.7%) up to two thirds (n = 1, 2.9%) of the circumference of the esophagus in the EVT group with four other leaks (n = 11.7%) in the pulled-up gastric tube along the longitudinal staple line or ischemia. These differences in the proportion of circumferential leak for SEMS and EVT were statistically significant (P = 0.001). Brangewitz *et al.*[20] also reported differences. Among the leaks in the EVAC group, 81.3% (n = 26) were at least 9 mm in diameter and the necrotic cavities could be accessed with the endoscope. In the stent-treated patients, 41% of leaks (n = 16) were smaller than the diameter of the endoscope and could not be intubated. Hwang *et al.*[16] showed no differences in the defect size. Data about the defect size were not available in another two manuscripts.

Regarding chronicity, Berlth *et al.*[15] reported a median 8 days between diagnosis and treatment for the EVT 8 (0–58) and the SEMS 8 (1–23) groups. Mennigen *et al.*[17] reported 7 days for EVT 7 (1–41) and SEMS 7 (1–20). Both demonstrated no differences between EVT or SEMS group. Hwang *et al.*,[16] Brangewitz *et al.*[20] and Schniewind *et al.*[24] did not provide data about chronicity.

Table 2 Adverse effects divided by population and article

Study, treatment method, *n* (%)	Migration, *n* (%)	Major bleeding, *n* (%)	Self-limiting bleed, *n* (%)	Tracheal injuries, *n* (%)	Stricture, *n* (%)	Perforation, *n* (%)	Ulcers, *n* (%)	Stent ingrowth, *n* (%)	Fatal outcome *n* (%)	Severity grade			
										Fatal	Severe	Moderate	Mild
Brangewitz *et al.*													
EVT – 32 (45)	5 (2)	1 (2.5)	0	1 (3)	3 (9)	0 (0)	0	NA	0	0	2	8	0
SEMS – 39 (55)	6 (15)	1 (2.5)	2 (5)	0 (0)	11 (28)	0 (0)	4 (10)	0	1 (2,5)	1	1	17	6
Schniewind *et al.*													
EVT – 17 (59)	ND	ND	ND	ND	ND	ND	ND	ND	ND	–	–	–	–
SEMS – 12 (41)	ND	ND	ND	ND	ND	ND	ND	ND	ND	–	–	–	–
Mennigen *et al.*													
EVT – 15 (33)	ND	ND	ND	ND	ND	ND	ND	ND	ND	–	–	–	–
SEMS – 30 (67)	ND	ND	ND	ND	ND	ND	ND	ND	ND	–	–	–	–
Hwang *et al.*													
EVT – 7 (38)	0 (0)	0	0	0	0	0	0	NA	0	0	0	0	0
SEMS – 11 (61)	3 (27)	0	0	0	0	0	0	3 (27)	0	0	0	6	0
Berlth *et al.*													
EVT – 34 (30)	4 (15)	0	0	0 (0)	1 (3)	0	0	NA	0	0	0	1	0
SEMS – 77 (70)	14 (20)	0	0	5 (6)	5 (7)	1 (1.2)	0	0	0	0	6	19	0

EVT, Endoscopic vacuum therapy; NA, not applicable; ND, no data; SEMS, Safety of self-expanding metal stents.

Endoscopic vacuum therapy demonstrated a 24% reduction in adverse events (RD 0.24, CI 0.13–0.35; $P = 0.0001$). The definition of adverse events was graded according to the American Society for Gastrointestinal Endoscopy (ASGE) lexicon as mild, moderate, severe, and fatal.[21] Excluding mild events, for which no intervention is needed, EVT also proves to be superior (RD 0.24, CI 0.13–0.35; $P = 0.0001$. The summary regarding migration, major bleeding, self-limiting bleeding, tracheal injuries, stricture, perforation, ulcers, stent ingrowth, and fatal outcome can be found in Table 2.

While the results of this study are promising, some limitations must be acknowledged. The major limitation of the present work is the absence of randomized clinical trials in the literature, which contributes to the high risk of bias of all included studies in this analysis. Besides that, the lack of standardization of clinical conditions can directly affect the results. Data about fistula size, laboratory studies, sepsis, antibiotics regimen, or an objective assessment through a predictive score system as APACHE system, could reduce the risk of bias. Standardization of techniques is another factor that hinders the external validity of the included works. Negative pressure regimens also varied in the included studies.[39,40] Additionally, the stents used for the treatment of upper gastrointestinal transmural defects were self-expanded metal stents and self-expanded plastic stents. In addition, many confounding variables interfere with the analysis. Standardization of intervention and hospital-based care protocols, as well as patient selection and randomization, will strengthen these results in future studies. Despite this, considering available data, there were no statistically significant differences between the groups, as shown in Table 1. Randomized studies, with a large volume of patients and standardized treatment and care protocols, are needed to reliably guide decision making in the future treatment of upper gastrointestinal transmural defects.

CONCLUSION

ENDOSCOPIC VACUUM THERAPY is a viable and safe alternative for the treatment of upper gastrointestinal transmural effects. The therapy presents high rates for successful defect closure and low complication indices, with its usage potentially associated with decreased mortality rates when compared to self-expandable metallic stents.

ETHICAL STATEMENT

THE STUDY WAS approved by the Research Ethics Committee of the University of São Paulo School of

Medicine Hospital das Clínicas and written consent was not required as this was a systematic review project.

DISCLOSURES

DRS. EPIFANIO SILVINO do Monte Junior, Diogo Turiani Hourneaux de Moura, Igor Braga Ribeiro, Kelly Elizabeth Hathorn, Galileu Ferreira Ayala Farias, Carolina Vaz Turiani, Flaubert Sena Medeiros and Wanderley Marques Bernardo have nothing to disclose. Dr. Eduardo Guimarães Hourneaux de Moura reports personal fees from Boston Scientific, personal fees from Olympus, outside the submitted work.

CONFLICT OF INTEREST

AUTHORS DECLARE NO conflict of interests for this article.

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Table S1 Assessment of quality of evidence using GRADEpro.