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REVIEW

Peroral Endoscopic Myotomy Is a Safe and Feasible Option in Management of Esophageal Diverticula: Systematic Review and Meta-Analysis

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Abstract

Esophageal diverticula can cause significant symptoms and affect the quality of life. There has been recent interest in the use of peroral endoscopic myotomy in the management of esophageal diverticula (D-POEM). In this meta-analysis, we have evaluated the efficacy and safety of D-POEM in the management of esophageal diverticula. Several databases were reviewed from inception to 6/19/2020 to identify the studies evaluating the feasibility, efficacy and safety of D-POEM in the management of esophageal diverticula. Our outcomes of interest were technical success, adverse events and difference in mean pre- and post-procedure symptom score. We performed subgroup analysis including patients with Zenker's diverticulum who underwent POEM (Z-POEM). Pooled rates with 95% confidence intervals (CI) for all outcomes were calculated using random effect model. We calculated standard mean difference (SMD) with 95% CI to compare mean pre- and post-procedure symptom score. We included 7 studies with 233 patients. For D-POEM, pooled rates (95% CI) for technical success and adverse events were 95% (91%, 97%) and 6% (3%, 10%) respectively. For Z-POEM, pooled rates (95% CI) for technical success and adverse events were 95% (90%, 97%) and 6% (3%, 10%) respectively. Mean post-procedure symptom score for all patients who underwent D-POEM was significantly lower compared to mean pre-procedure symptom score, SMD (95% CI) 2.17 (1.51, 2.83). This meta-analysis demonstrated that D-POEM is a safe and feasible option for patients with symptomatic esophageal diverticula.

Keywords Peroral endoscopic myotomy · Esophageal diverticula · Zenker's diverticulum · Meta-analysis

Introduction

Esophageal diverticula can cause symptoms such as dysphagia, aspiration, regurgitation or chest pain affecting the quality of life [1]. Esophageal diverticula are classified into three types based on pathophysiology and location in esophagus: Zenker's, mid-esophageal, and epiphrenic diverticula [2]. Surgical management of esophageal diverticula is associated with good long-term outcomes, but the need for general anesthesia and substantial morbidity associated with surgery limits it usefulness [3, 4]. Flexible endoscopic septum division (FESD) has shown promising results in the management of Zenker's diverticula largely replacing surgical and

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rigid endoscopic treatments. One meta-analysis found that FESD was a safe and effective option in the management of Zenker's diverticulum with pooled success and adverse events rates of 91% and 11% respectively [5].

Since its introduction in 2009, peroral endoscopic myotomy (POEM) has been successfully used in the management of achalasia and gastroparesis. There has been a recent interest in the use of POEM in the management of esophageal diverticula (D-POEM) which is a breakthrough in third space endoscopy. Studies have evaluated the efficacy of D-POEM and have shown promising results [6, 7]. Some studies have compared D-POEM with flexible endoscopic diverticulotomy and have shown higher clinical success with D-POEM [8]. Whether D-POEM will become the treatment of choice for esophageal diverticula in future is an important question. To answer this question and evaluate the efficacy and safety of D-POEM in the management of esophageal diverticula, we conducted this systematic review and meta-analysis.

Methods

Data Sources and Search Strategy

We followed the guidelines of Preferred Reporting items for Systematic Review and Meta-Analysis (PRISMA) [9] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [10]. The PRISMA checklist is provided in supplementary Table 1. An experienced medical librarian (W. L-S.) conducted a comprehensive search of several databases including PubMed and MEDLINE, Embase, Web of Science Core Collection and the Cochrane Central Register of Controlled Trials from inception to 06/19/2020. There was no limitation of language in conducting the search. The search included truncation-expanded keywords and database-specific subject headings for the concepts of POEM combined with either "Zenker" or esophageal diverticula. The search included following keywords: (Per-oral-endoscopic-myotom* OR Peroral-endoscopic-myotom* OR POEM OR D-POEM OR Z-POEM OR DPOEM OR ZPOEM OR ((Peroral OR Oral OR esophag* OR pharyng* OR transpharyng*) AND (Natural Orifice-Endoscopic-Surgery OR natural-orifice-transluminal-endoscopic-surgery))) AND (divertic* OR zenker*). The full search strategies from all databases are provided in supplementary Fig. 2. We also manually searched for abstracts with relevant data from DDW from 2014 to 2019.Two authors (FK and SS) independently reviewed the titles and abstracts of the articles retrieved from search and excluded articles that did not address our question of interest. Full texts of remaining articles including references were reviewed. The search strategy is illustrated in Fig. 1.

Inclusion and Exclusion Criteria

Two authors (FK and MAK) independently reviewed original studies based on pre-established inclusion criteria detailed below. We included studies which evaluated the feasibility, efficacy, and/or safety of D-POEM in the management of all esophageal diverticula including Zenker's, mid-esophageal, and epiphrenic. We excluded case reports, case series with fewer than five patients, guidelines, editorials, review articles, and studies with animal models. If there were multiple publications from the same cohort, we included only the most recent publication and/or the publication with more information. We included full publications as well as abstracts. All articles were downloaded into Endnote X9.0, a bibliographic database manager. Duplicate citations were removed.

Data Extraction and Quality Assessment

Two authors (FK and MAK) independently assessed the eligibility of included studies and designed data extraction forms and then collected data independently using these forms. Any discrepancy was resolved by a re-review of the data and discussion with a third author (DGA). Data extracted included year and country of publication, type of study, patient demographics, number of patients, duration of follow-up, inclusion and exclusion criteria, type of scoring system used to assess response to treatment (such as Eckardt score and Dakkak and Bennett score), technical success, clinical success, adverse events, pre- and post-treatment symptom score, operative time, length of stay, size of diverticula, recurrence of symptoms, and re-intervention.

We performed quality assessment of studies using a modified version of the Newcastle–Ottawa Scale (NOS), which allocates maximum of six points [11]. On this scale, high-quality studies score over 3 while low-quality studies score 3 or below. Two authors (FK and HM) independently performed the quality assessment and any disagreement was discussed with a third reviewer (DGA).

Data Synthesis and Statistical Analysis

Our outcomes of interest were technical success (defined as successful completion of all steps of the procedure), adverse events, and difference in mean pre- and post-procedure symptom score (based on Eckardt score or Dakkak and Bennett score). We performed a subgroup analysis by including full publications only and excluding abstracts. We also performed subgroup analysis for patients with Zenker's diverticulum who underwent POEM (Z-POEM) and analyzed technical success, adverse events, and difference in

Table 1 Characteristics of studies

Study, year	Number of patients	Number of males	Type of diverticula	Follow-up (months) mean or median	Definition of clinical success	Number of operators	Inclusion criteria	Exclusion criteria	NOS score
Zeng et al, 2020	10	7	Zenker's= 2, mid-esophagus = 5, epiphrenic = 3	11.0 (10.25–17.25)	Reduction in symptoms on a new symptomatic scoring system based on Dakkak and Bennett score and Eckardt score	NA	Patients with symptomatic esophageal diverticulum who underwent D-POEM were included	NA	4
Yang et al, 2020	75	42	Zenker's= 75	9.72 (3.45, 14.5)	Complete or near-complete resolution of post-procedure dysphagia (Dakkak and Bennett score, 0 or 1) without the need for repeat endoscopic or surgical intervention during follow-up	NA	Patients who underwent Z-POEM were included. ZDs were diagnosed on imaging studies, including barium esophagram and/or CT, and confirmed by endoscopy	Patients with <30 days of follow-up and those with ZD in the setting of esophageal motility disorders were excluded.	5
Maydeo et al 2019	25	18	Zenker's = 20, epiphrenic = 5	12	Complete or near-complete resolution of symptoms, without need for repeat intervention at follow-up (modified Eckardt score of < 3)	1	Age ≥18, severe disease defined as two or more hospitalizations within 1 year for symptoms related to bronchoaspiration	Patients with a recent endoscopy (<3 months) showing evidence of tumor in the esophagus, coagulation abnormalities, decompensated liver disease, anesthesia risk, and refusal to give consent	5
Basile et al, 2020	7	3	Epiphrenic = 7	12	Complete or partial regression of dysphagia	NA	Patients referred for symptomatic pulsion esophageal diverticula located in the mid- or lower esophagus and associated with esophageal dysmotility	NA	5
Li et al, 2019	8	5	Epiphrenic = 8	12	Improvement in the modified Eckardt scale measured before and after procedure	1	Patients who were diagnosed with epiphrenic diverticula and underwent D-POEM at Jiangsu Province Hospital and Changzhou No.2 People's Hospital in China	Patients with prior treatment interventions were excluded	5

Table 1 (continued)

Study, year	Number of patients	Number of males	Type of diverticula	Follow-up (months) mean or median	Definition of clinical success	Number of operators	Inclusion criteria	Exclusion criteria	NOS score
Alghamdi et al, 2020 Abstract	91	NA	Zenker's= 91	5.25	Decrease in Dakkak and Bennett dysphagia score to 1; and to 0 in patients with baseline score of 1; and complete resolution of other symptoms if no dysphagia at baseline	NA	Patients who underwent Z-POEM for the management of ZD were included	NA	4
Kahaleh et al, 2020 Abstract	17	NA	Zenker's= 17	NA	Reduction in Eckardt score	NA	Patients who underwent endoscopic management of Zenker's Diverticulum either by Z-POEM from 5 international academic centers were included	NA	3

NA: Not available or not applicable

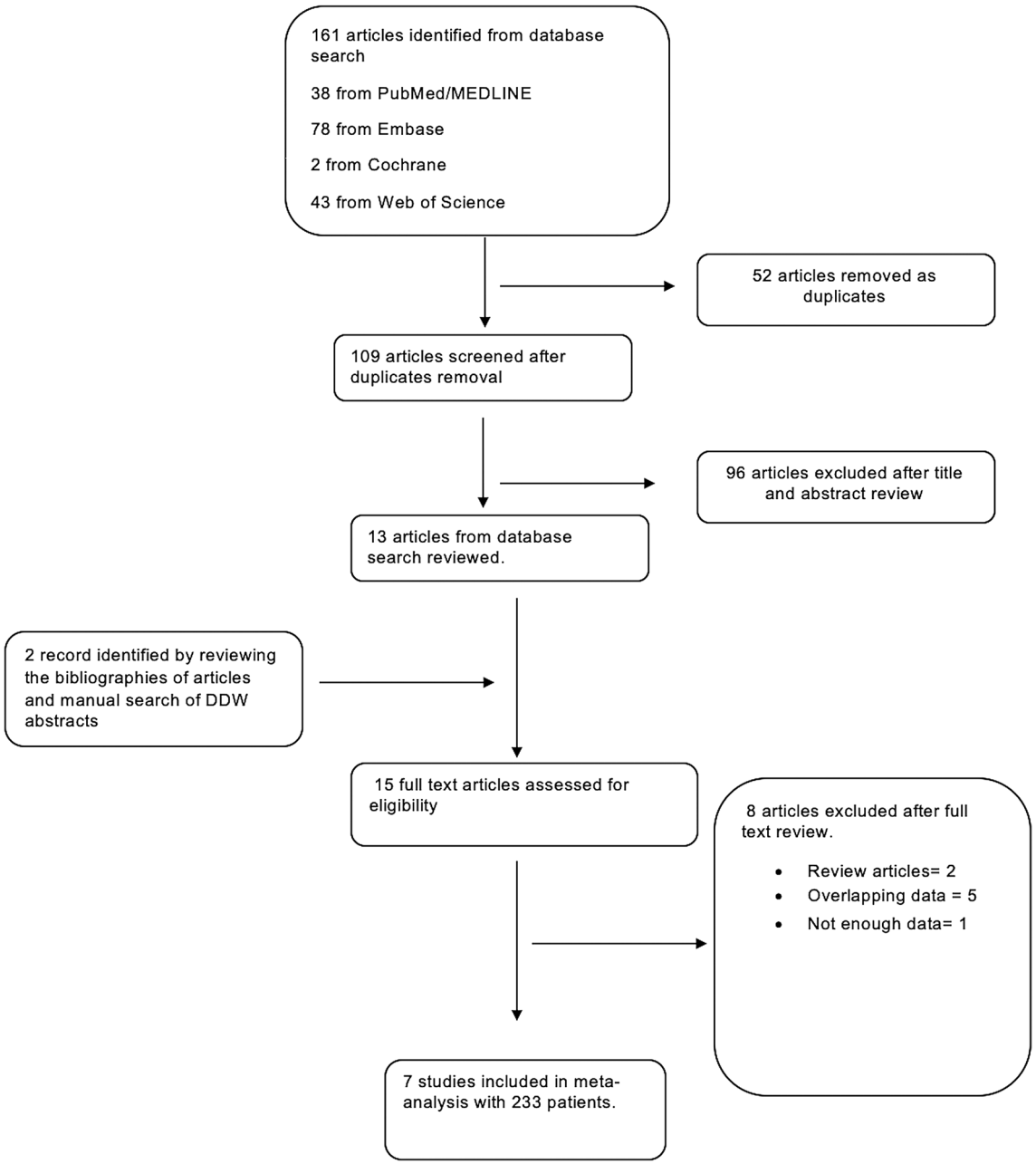

Fig. 1 PRISMA flowchart

pre- and post-procedure symptom score. Two studies did not report the size of esophageal diverticula and were excluded from the analysis of technical success [6, 12]. We did not analyze the clinical success rate because the definition of clinical success varied across studies. Details of definition of clinical success by each study are provided in Table 1.

We calculated pooled rates with 95% confidence intervals (CI) for technical success and adverse events. We calculated standard mean difference (SMD) with 95% CI to compare pre- and post-procedure symptom score. We used a random effect model for our analyses. Heterogeneity was assessed by I^2 statistic. The statistical analysis was performed using comprehensive meta-analysis (CMA) software.

Results

Search Strategy Yield and Quality Assessment

The search strategy yielded 115 articles; of these, we removed 6 duplicates (Fig. 1). Of the remaining 109 articles, 96 were removed after title and abstract review. Two articles were

identified by reviewing the bibliographies of articles and from manual search of DDW abstracts. We reviewed the full texts of 15 articles from which we ultimately included 7 studies comprising 233 patients [6–8, 12–15]. Three studies with 183 patients exclusively included patients with Zenker's diverticula [7, 8, 15]. The characteristics of included studies are summarized in Tables 1 and 2. Quality assessment of studies is summarized in Table 1.

Meta-Analysis

Technical Success

The pooled rate (95%CI) of technical success among patients undergoing D-POEM was 95% (91%, 97%) with no heterogeneity ($I^2=0\%$) (Fig. 2). Subgroup analysis including full publications only found that the pooled rate of technical success of D-POEM was 97% (92%, 99%), $I^2=0\%$. Subgroup analysis including patients who underwent Z-POEM showed that the rate of technical success of Z-POEM was 95% (90%, 97%), with no heterogeneity ($I^2=0\%$).

Adverse Events

The pooled rate (95%CI) of adverse events among patients undergoing D-POEM was 6% (3%, 10%), with no heterogeneity ($I^2=0\%$) (Fig. 3). Subgroup analysis including full publications only showed that the rate of adverse events with D-POEM was 6% (3%, 12%), $I^2=0\%$. Subgroup analysis including patients who underwent Z-POEM found that the rate of adverse events with Z-POEM was 6% (3%, 11%), with no heterogeneity ($I^2=0\%$).

Pre- and Post-procedure Symptom Score

In this analysis, we calculated the difference in mean symptom score (based on the Eckardt score or the Dakkak and Bennett score) before and after procedure and reported it as SMD. We found that the mean post-procedure symptom score in patients who underwent D-POEM was significantly lower compared to mean pre-procedure symptom score, SMD (95% CI) 2.17 (1.51, 2.83), $I^2=68\%$. Subgroup analysis including patients who underwent Z-POEM also showed that the mean post-procedure symptom score was significantly lower when compared to the mean pre-procedure symptom score, SMD (95% CI) 2.34 (1.31, 3.37).

Discussion

Esophageal diverticula are rare, but they can cause significant symptoms and affect quality of life. Surgical management of esophageal diverticula involves the complete

Table 2 Data on primary and secondary outcomes of interest

Study, year	Number of patients	Technical success	Clinical success	Size of diverticula (mm) Mean or median	Adverse events	Operative time Mean or median	Length of stay	Recurrent symptoms	Re-intervention	Pre-op symptom score	Post-op symptom score
Zeng et al, 2020	10	11	9	NA	1=subcutaneous emphysema	38.9 ± 20.5	8.8 ± 1.8	0	NA	2.5 (2.00–3.25)	1.0 (0-1.25)
Yang et al, 2020	75	73	69	31.3 ± 1.6	Total= 5, Bleeding= 1 perforations= 4	52.4 ± 2.9	1.8 ± .2	1	1	1.96±0.68	0.25 ± 0.52
Maydeo et al, 2019	25	25	19/22	50 (40–70)	0	36 (25 –45)	5 (4–10)	NA	NA	2.8±0.3	1.8±0.8
Basile et al, 2020	7	7	6	NA	0	NA	3-8	NA	NA	NA	NA
Li et al, 2019	8	8	8	36.8 (15.9)	0	52.87±22.47	5.87±0.83	0	NA	6.88 ± 3.04	1.38±1.41
Alghamdi et al, 2020	91	85	79	30	6, details not provided	43	1	NA	NA	1.7±0.9	NA
Kahaleh et al, 2020	17	17	15	30-49	0	38.2±15.1	1.57±1.12	1	1	3.36±2.22	0.38±0.74

NA: Not available or not applicable

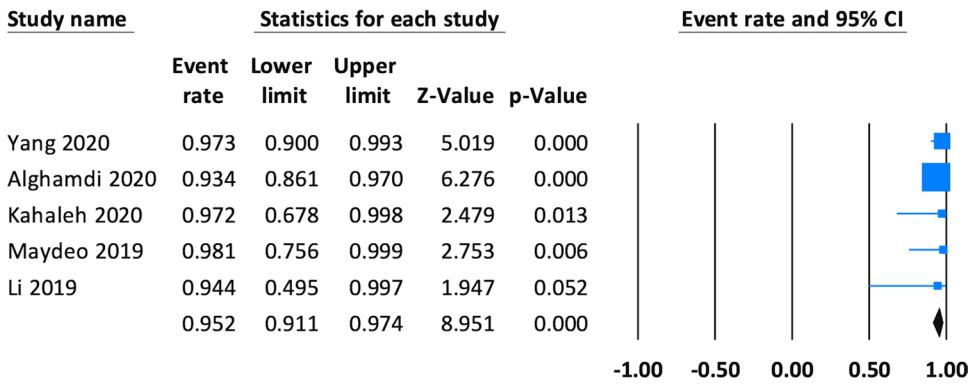

Fig. 2 Technical success of D-POEM

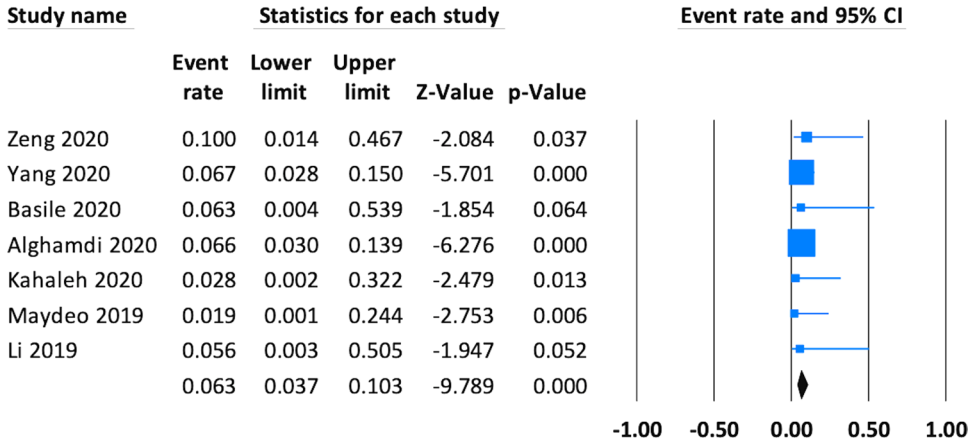

Fig. 3 Adverse events of D-POEM

resection of the diverticulum; this is more invasive than endoscopic options and has a high associated rate of adverse events [16]. The use of D-POEM is relatively a new concept and some studies have shown that it is an effective option for all esophageal diverticula.

Z-POEM has some potential advantages over FESD. In contrast to FESD, where the aim is to achieve a partial myotomy of cricopharyngeal muscle tissue, Z-POEM allows better exposure of the muscle and a complete myotomy, decreasing the risk of both treatment failure and symptom recurrence. In Z-POEM, septum transection is performed using a submucosal tunneling approach which enables complete exposure and division of the septum in one session. One previous meta-analysis evaluating the efficacy and safety of FESD for Zenker's diverticula found that the rate of adverse events with FESD was 11% which is significantly higher compared to rate of adverse events with Z-POEM (6%) as found in our meta-analysis [5].

Epiphrenic diverticula are often more challenging to manage due to the high risk of complications associated with their surgical management. One meta-analysis found that the rate of complications for epiphrenic diverticula after surgery was 21% [16]. This study noted that the most common complication was a leak at the staple line which required repeat surgery in almost two-thirds of cases. D-POEM may be particularly advantageous in cases of epiphrenic diverticula because they are usually associated with esophageal motility disorders such as a non-relaxing lower esophageal sphincter [12]. Use of D-POEM in these cases may be beneficial as it can potentially and simultaneously treat the underlying motility disorder as well as the diverticulum.

This is the first meta-analysis to evaluate the feasibility and safety of D-POEM. However, this study has limitations. All the studies included were observational in nature and have the risk of measured and unmeasured confounding due to lack of randomization [17]. Our sample size is relatively small so the analysis may be underpowered. The analysis of difference of pre- and post-procedure symptom score was limited by the fact that some studies reported symptom score (based on the Eckardt score or the Dakkak and Bennett score) as mean and others as median, and we only included the studies which reported this score as mean. Another limitation to analyzing symptom scores was significant heterogeneity, which was encountered in the data and is possibly due to the use of different scoring systems in different studies ($I^2 = 68\%$). Otherwise, we did not find any significant heterogeneity in the analysis of all other outcomes. We could not perform a formal analysis of clinical success because the definition of clinical success was different in different studies. Finally, the number of operators and skills, experience,

and level of expertise of each operator were not reported in most of the studies. This is an important issue because these factors can affect the outcomes of endoscopic procedures.

Overall, this meta-analysis demonstrates that D-POEM is a safe and feasible option for patients with symptomatic esophageal diverticula.

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Compliance with Ethical Standards

Conflict of interest The authors have no relevant conflicts of interest.

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