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Endoscopic stapler versus laser diverticulotomy for Zenker's diverticulum: a systematic review and meta-analysis

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Review Article

Mr Daniel Edwards takes responsibility for the integrity of the content of the paper

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Abstract

Objective. A literature review and meta-analysis was performed to assess for difference in rate of complications and need for revision surgery between endoscopic stapler-assisted diverticulotomy and endoscopic carbon dioxide laser diverticulotomy. The hypothesis was that endoscopic stapler-assisted diverticulotomy has a lower complication rate but endoscopic carbon dioxide laser diverticulotomy has a lower need for revision surgery.

Method. This was a systematic review of English-language studies comparing endoscopic stapler-assisted diverticulotomy and endoscopic carbon dioxide laser diverticulotomy for the treatment of Zenker's diverticulum. Meta-analysis of results with regard to rate of pharyngeal perforation, major post-operative complication and need for re-operation was performed.

Results. Nine retrospective studies were included with pooled analysis of 417 endoscopic stapler-assisted diverticulotomy and 413 endoscopic carbon dioxide laser diverticulotomy cases. Meta-analysis found no significant difference in rate of pharyngeal perforation, major complication or need for re-operation between the two groups.

Conclusion. This study demonstrated both endoscopic stapler-assisted diverticulotomy and endoscopic carbon dioxide laser diverticulotomy to be a safe alternative to open surgery for Zenker's diverticulum. Both appear to be similar in terms of adverse events and efficacy. The authors recommend either approach, guided by surgeon's preference and experience, where patients are unsuitable for an open surgery approach.

Introduction

Pharyngeal pouch (Zenker's diverticulum) is an acquired pseudodiverticulum of the mucosa of the hypopharynx, through the point of least muscular support between the cricopharyngeus and thyropharyngeus muscle (Killian's dehiscence). Zenker's diverticulum is likely to recur less frequently when treated by open myotomy with or without pouch excision, but it is accepted that an endoscopic diverticulotomy approach produces good results with a reduced morbidity and duration of in-patient stay.[1] This, coupled with patients often being older adults and the co-morbid nature of the Zenker's diverticulum patient group, means that many ENT surgeons will advocate for an endoscopic approach as the treatment of choice for Zenker's diverticulum, especially given the pertinent need for efficient use of operating theatre time and in-patient beds in the modern British healthcare system.

Previous literature has suggested endoscopic stapler-assisted diverticulotomy to be associated with a lower risk of morbidity from oesophageal perforation, mediastinitis and bleeding,[2] but has suggested endoscopic carbon dioxide laser diverticulotomy to reduce the need for revision surgery, especially when used for revision cases.[3] In 2014, a systematic review and meta-analysis by Parker and Misono found no difference between endoscopic stapler-assisted diverticulotomy and endoscopic carbon dioxide laser diverticulotomy in terms of overall complications and rate of revision surgery, although the included series had low case numbers.[4]

In the experience of the authors, both endoscopic stapler-assisted diverticulotomy and endoscopic carbon dioxide laser diverticulotomy are effective. Endoscopic stapler-assisted diverticulotomy is often reported to be quick to perform and easy to learn, but in cases with poor access, accurate positioning of the stapler device can be problematic. Some surgeons describe difficulty dividing the distal portion of a cricopharyngeal bar using modern stapler devices. Endoscopic carbon dioxide laser diverticulotomy arguably has a steeper learning curve but can afford a better view in cases with difficult access.

There is currently no consensus as to whether endoscopic stapler-assisted diverticulotomy or endoscopic carbon dioxide laser diverticulotomy is the treatment of choice for Zenker's diverticulum; we aim to review the contemporary literature and perform a meta-analysis to assess for difference in rate of complication and need for revision surgery. We hypothesised that endoscopic stapler-assisted diverticulotomy has a lower

complication rate, but endoscopic carbon dioxide laser diverticulotomy has a lower need for revision surgery.

Materials and methods

Inclusion criteria

This review included English-language articles on adult human patients comparing the outcomes of a group of patients undergoing endoscopic stapler-assisted diverticulotomy with a group of patients undergoing endoscopic carbon dioxide laser diverticulotomy, with or without other treatment arms.

Method

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') statement[5] was used to guide the review. A search of the PubMed and Ovid Medline databases was carried out. Broad title search terms were used prior to screening: 'Pharyngeal pouch', 'Zenker's/Zenker/Zenkers diverticulum', 'diverticulotomy', 'diverticulostomy' and 'diverticulectomy'.

References of relevant review articles were screened. Duplicates were removed prior to screening of results for relevance by title and abstract. Data from centres with a very low throughput of cases performed using a particular technique were considered unlikely to be representative of the true complication rate of endoscopic stapler-assisted diverticulotomy or endoscopic carbon dioxide laser diverticulotomy. Because of this potential bias, papers with less than 20 cases in a treatment arm were excluded. The selection process is illustrated in Figure 1.

Primary outcomes of rate of re-operation, pharyngeal leak or perforation, and non-dental complication were recorded for each study. Meta-analysis was performed in a blinded manner. Two sets of raw data were prepared, masking which surgical technique was to be used as a control during statistical analysis. Masking was broken during final preparation of the manuscript.

Descriptive statistics were used to summarise demographic data and study characteristics. Odds ratio and 95 per cent confidence intervals (CIs) were obtained for each primary outcome in each article. Consistency has been explored in each analysis by means of I^2. An inverted variance with random effects model with proportional correction for zero events was used. Inverted variance with fixed effects was used if no heterogeneity was present. In order to assess publication bias across studies, funnel plots and Egger tests were used. Analysis was conducted using Stata statistical analysis software (version 15.0; Statacorp, College Station, USA) using Mar command software for meta-analysis. Some secondary outcomes could not be subject to meta-analysis; these will be described in the discussion.

Results

A total of 1022 articles were identified in the initial search. Exclusion of duplicates and irrelevant articles left 53 articles comparing surgical technique for Zenker's diverticulum. Of

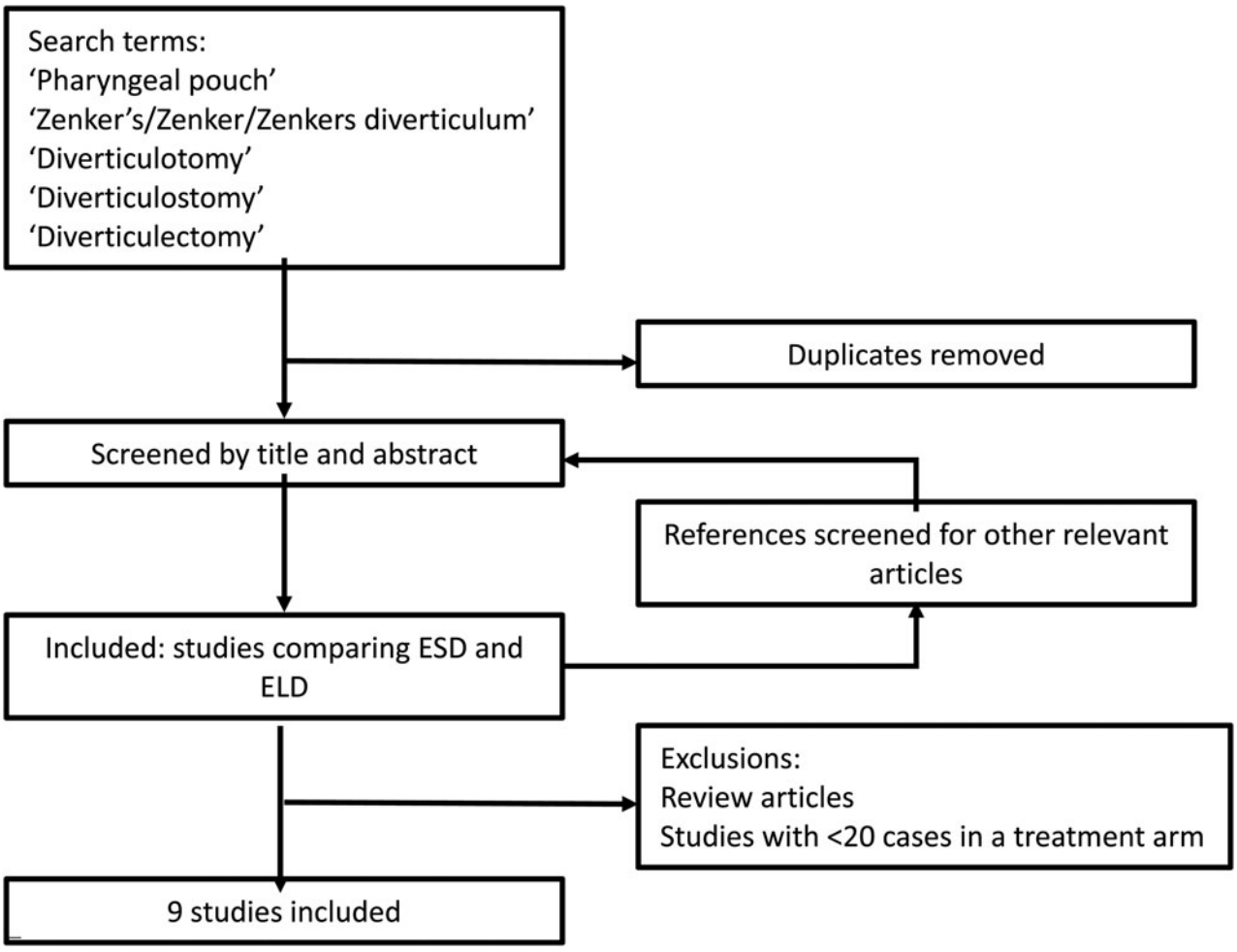

Fig. 1. Selection process for the systematic review. ESD = endoscopic stapler-assisted diverticulotomy; ELD = endoscopic carbon dioxide laser diverticulotomy

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these, 20 compared endoscopic stapler-assisted diverticulotomy and endoscopic carbon dioxide laser diverticulotomy in sufficient numbers. Six review articles were excluded. Five comparative studies were excluded as they included less than 20 cases in a treatment arm.[6–10] Nine retrospective studies were included[11–19] with a total of 830 cases; 417 patients underwent endoscopic stapler-assisted diverticulotomy, and 413 underwent endoscopic carbon dioxide laser diverticulotomy. No prospective studies could be included.

Study characteristics

Characteristics of included studies are summarised in Table 1. Cases underwent operations over a period from 1984 to 2015 and articles were published between 2002 and 2016, reflecting the relatively low incidence of Zenker's diverticulum. Articles were exclusively from developed-world healthcare systems in Australia, North America and Northern Europe. Each article described cases operated on at different centres, but two articles had common authorship.[14,17] Three of nine articles compared only endoscopic stapler-assisted diverticulotomy to endoscopic carbon dioxide laser diverticulotomy[16,17,19]; three articles included a treatment group that had undergone non-specified transcervical surgery[11,14,15]; and three compared endoscopic stapler-assisted diverticulotomy, endoscopic carbon dioxide laser diverticulotomy and open diverticulectomy with or without cricopharyngeal myotomy.[12,13,18] We have not commented on transcervical surgery for Zenker's diverticulum as it does not relate to the hypothesis being tested.

Four articles did not describe length of follow up.[11,12,14,17] Among the remaining articles, minimum follow-up period varied significantly. Data collection was by case note review in all articles; in addition, two articles used telephone interviews[13,18] and two used postal questionnaires[16,17] to gain information about post-operative symptoms.

Surgical techniques were broadly similar between endoscopic stapler-assisted diverticulotomy and endoscopic carbon dioxide laser diverticulotomy treatment groups. Differences between studies with regards to stapler device and diverticuloscope are described in Table 1.

Study bias

Two reviewers (DE, CT) independently used the Risk of Bias in Non-Randomised Studies of Interventions[20] tool to subjectively assess for risk of bias in each included article. Where reviewers disagreed on the level of bias, the more critical assessment was accepted. The Risk of Bias in Non-Randomised Studies of Interventions tool allows assessors to classify risk of bias as 'low', 'moderate', 'serious' or 'critical'. Risk of bias in selected articles ranged from 'moderate' to 'serious'. A number of articles demonstrated baseline confounding because in some cases the rationale for selection of patients to each treatment group was not specified. In other cases, it was based on factors also considered to be prognostic variables, for example, size of Zenker's diverticulum,[13] failure of alternate surgical technique,[16] or frailty and medical co-morbidity.[11] Discrepancy in post-intervention management between treatment groups was another frequently encountered source of bias. Although some studies described a standard post-operative regimen for all patients,[11,14] one reported routine post-operative imaging of endoscopic carbon dioxide laser diverticulotomy but not endoscopic stapler-assisted diverticulotomy cases,[17] and another reported differences in post-operative fasting period between groups.[19] Although all articles had at least a 'moderate' risk of bias, we considered this to be expected in a group of retrospective non-randomised studies of intervention and will describe the likely direction of bias in our discussion.

Pharyngeal perforation

The incidence of post-operative pharyngeal leak or perforation was reported in each article, but definitions varied. Four studies did not specify how a leak was diagnosed.[11,12,14,16] Verhaegen *et al.* defined leak by radiological findings.[17] Three studies defined presence of leak based on clinical findings,[13,18,19] and Leibowitz *et al.* described the clinical sequelae of leak, namely pneumomediastinum and retropharyngeal abscess.[15] Management of leak was not consistently described. Pharyngeal leak was described in 12 of 417 endoscopic stapler-assisted diverticulotomy cases (2.9 per cent) versus 13 of 413 endoscopic carbon dioxide laser diverticulotomy cases (3.1 per cent). The risk of leak in the study group compared with the control group had an odds ratio of 0.83 (95 per cent CI = 0.34 to 2.01). We did not appreciate a difference between treatment groups based on these results. In each study, the confidence interval included an odds ratio equal to one. Six of the studies had zero events in at least one treatment arm and proportional continuity correction was applied. Inverse of variance for random effects was applied (I^2 = per cent of variation because of heterogeneity; $I^2 = 0$ per cent). The heterogeneity was less than 25 per cent. Funnel and forest plots for odds ratio of pharyngeal perforation in each study are shown in Figure 2. Egger test showed a lack of publication bias ($p > 0.1$).

Recurrence and need for re-operation

Two studies reported rate of recurrence of Zenker's diverticulum. Recurrence was not specifically defined by Visser *et al.*[14] but was defined as persistent symptoms requiring a change in diet or re-operation by Leibowitz *et al.*[15] Rate of re-operation was reported by 7 studies;[11–14,16,17,19] 51 of 317 (16.1 per cent) and 46 of 293 (15.7 per cent) endoscopic stapler-assisted diverticulotomy and endoscopic carbon dioxide laser diverticulotomy cases, respectively, required re-operation. The re-operation risk in the study group compared with the control group had an odds ratio of 1.13 (95 per cent CI = 0.57 to 2.25). Based on these results, a difference between groups was not appreciated. In each study, the confidence interval included an odds ratio equal to one. Two of the studies had zero events in a treatment group and proportional continuity correction was applied. Inverse of variance for random effects was applied (I^2 = per cent of variation because of heterogeneity; $I^2 = 19.3$ per cent (95 per cent CI = 0 per cent to 61.0 per cent). The heterogeneity was less than 25 per cent. Funnel and forest plots for odds ratio of re-operation in each study are shown in Figure 2. Egger test showed a lack of publication bias ($p > 0.1$).

Other major complications

The rate of dental complication was not subject to meta-analysis because of the heterogenicity in diverticuloscope used between studies. The review identified no cases of post-operative mortality. Major complications reported included post-operative bleeding,[11,16,17] quadriparesis,[15] and one incidence of vocal fold paralysis in each of the endoscopic stapler-

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Table 1. Study characteristics

Study	Patients (*n*)			Age (mean ± SD or median (range); years)		Treatment arms	Surgical technique	Follow up	Complications
	Total	ESD	ELD	ESD	ELD				
Veivers, 2015[11]	135	35	42	78.5 ± 12	70.7 ± 12.9	ESD, ELD, open surgery	Holinger-Benjamin diverticuloscope, Ethicon Endopath ETS ATW45 stapler; 4W CO_2 laser	Not stated	Re-operation: ESD, 7 (20%); ELD, 6 (14%). Perforation: ESD, 0 (0%); ELD, 4 (10%)
Yeo & Mackenzie, 2010[12]	100	58	26	Median: 70 (range, 36–89)		ESD, ELD, open diverticulectomy, cricopharyngeal myotomy, endoscopic dilatation	Not stated	Not stated	Re-operation: ESD, 7 (12%); ELD, 4 (15%). Perforation: ESD, 2 (3%); ELD, 0 (0%)
Shah *et al*., 2016[13]	62	35	27	Median: 70 (range, 34–92)		ESD, ELD, open diverticulectomy with cricopharyngeal myotomy	Not stated	Median, 1.6 years	Re-operation: ESD, 6 (17%); ELD, 0 (0%). Perforation: ESD, 1 (3%); ELD, 1 (3%)
Visser *et al*., 2016[14]	94	42	33	72 ± 11.5	69 ± 9.6	ESD, ELD, open surgery	Van Overbeek diverticuloscope, Endo-GIA 30 stapler; Dohlman laryngoscope and CO_2 laser	Not stated	Re-operation: ESD, 12 (29%); ELD, 7 (21%). Perforation: ESD, 4 (10%); ELD, 0 (0%)
Leibowitz *et al*., 2014[15]	164	69	68	Mean: 74.45	Mean: 74.71	ESD, ELD, open surgery	Not stated	Minimum 12 months	Re-operation: Not stated. Perforation: ESD, 2 (3%); ELD, 2 (3%)
Murer *et al*., 2015[16]	74	45	29	75 (45–93)	73 (57–90)	ESD, ELD	Weerda diverticuloscope, sawn-off Endo-GIA 30 stapler and micro-scissors; non-spreadable diverticuloscope and CO_2 laser	Mean, 4.7 years (1.1–10.5)	Re-operation: ESD, 3 (7%); ELD, 5 (17%). Perforation: ESD, 0 (0%); ELD, 0 (0%)
Verhaegen *et al*., 2011[17]	107	35	72	69.7 (42–97)	64.9 (42–91)	ESD, ELD	Van Overbeek/Weerda diverticuloscope, sawn-off Endo-GIA 30 stapler; Weerda diverticuloscope, Sharplan 30C laser	Not stated	Re-operation: ESD 9 (26%); ELD 24 (33%). Perforation: ESD, 0 (0%); ELD, 0 (0%)
Gutschow *et al*., 2002[18]	187	31	55	75 (39–92)	71 (41–87)	ESD, ELD, transcervical cricomyotomy with or without resection, transcervical resection alone, transcervical myotomy with or without diverticulopexy	Weerda diverticuloscope, sawn-off Endo-GIA 30 stapler; Holinger-Benjamin diverticuloscope, 1040 Sharplan laser	1–129 months	Re-operation: Not stated. Perforation: ESD, 0 (0%); ELD, 2 (4%)
Adam *et al*., 2012[19]	128	67	61	Mean: 70.1	Mean: 69.9	ESD, ELD	Weerda diverticuloscope with or without oesophageal dilatation; Endo-GIA 30 stapler, CO_2 laser 7W continuous	Minimum 6 months	Re-operation: ESD, 7 (10%); ELD 0 (0%). Perforation: ESD, 3 (4%); ELD, 4 (7%)

ESD = endoscopic stapler-assisted diverticulotomy; ELD = endoscopic carbon dioxide laser diverticulotomy

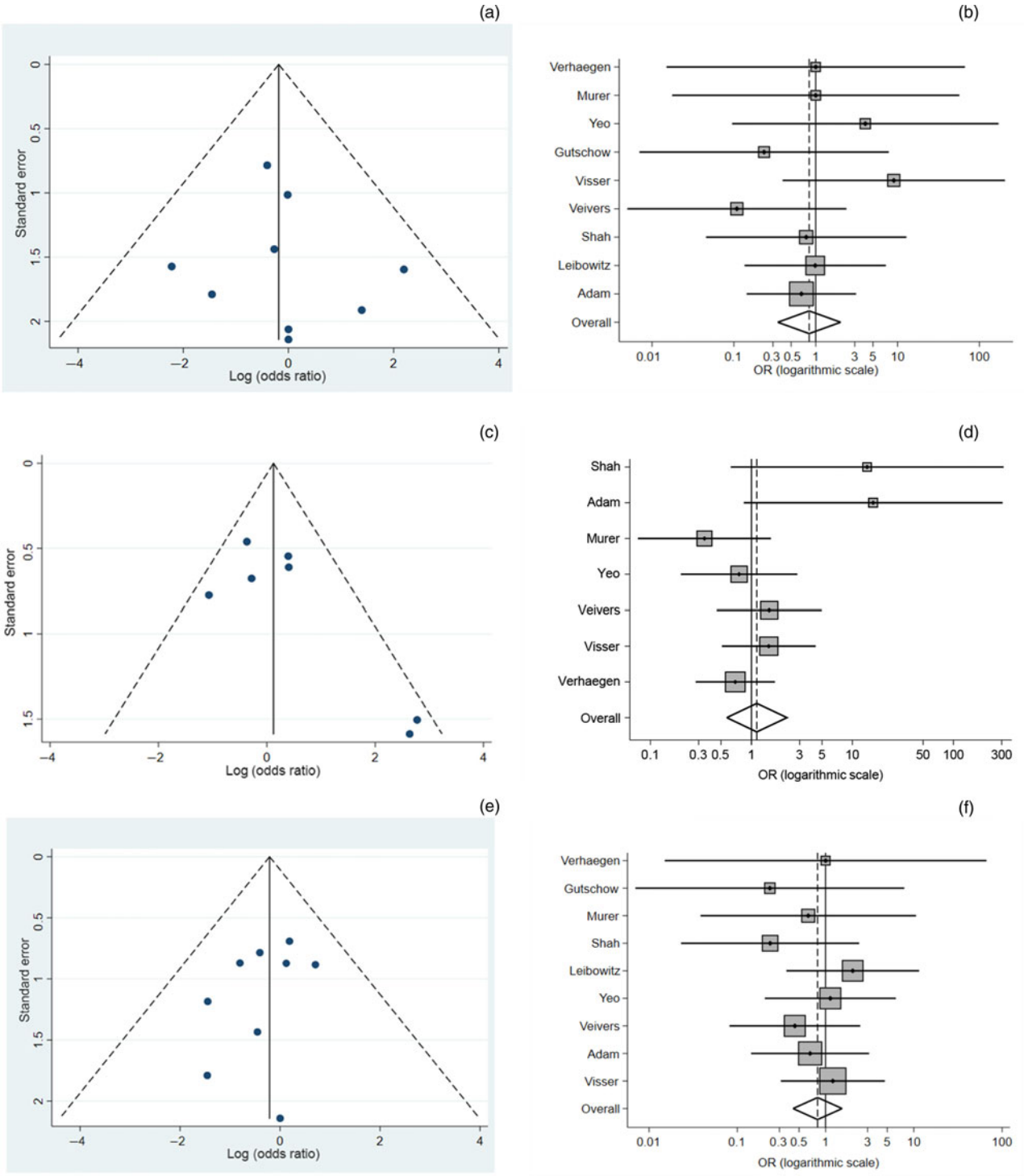

Fig. 2. Comparison of endoscopic stapler-assisted diverticulotomy (ESD) and endoscopic carbon dioxide laser diverticulotomy (ELD) showing: (a) funnel and (b) forest plots showing difference in odds ratio of pharyngeal perforation following ESD compared with ELD; (c) funnel and (d) forest plots showing difference in odds ratio of re-operation following ESD compared with ELD; and (e) funnel and (f) forest plots showing difference in odds ratio of major complications following ESD compared with ELD. OR = odds ratio

assisted diverticulotomy and endoscopic carbon dioxide laser diverticulotomy groups.[11,14] These were grouped with cases of perforation and their sequelae for analysis of odds ratio of major post-operative complication. The risk of major complication in the study group compared with the control group had an odds ratio of 0.81 (95 per cent CI = 0.43 to 1.54). A difference between groups was not appreciated. In each study, an odds ratio of one was within confidence intervals. Two of the studies had zero events in at least one treatment arm and proportional continuity correction was applied. Inverse of variance for random effects was applied (I^2 = per cent of variation because of heterogeneity; $I^2 = 0$ per cent). The heterogeneity was less than 25 per cent. Funnel and forest plots for odds ratio of major post-operative complication in each study are shown in Figure 2. Egger test showed a lack of publication bias ($p > 0.1$). The findings of the meta-analysis are summarised in Table 2.

Certainty of evidence

The Grades of Recommendation, Assessment, Development and Evaluation ('GRADE') working group system[21] was used

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Table 2. Summary of findings

Outcome	Relative effect for ESD compared to ELD (OR (95% CI))	Participants (*n*)	Certainty of the evidence (GRADE)	Comments
Pharyngeal perforation	0.83 (0.34–2.01)	830, 9 studies	Low*	No significant difference between groups detected
Re-operation	1.13 (0.57–2.25)	610, 7 studies	Low*	No significant difference between groups detected. Re-operation used as surrogate measure for recurrence
Other major complication	0.81 (0.43– 1.54)	830, 9 studies	Low*	No significant difference between groups detected
Mortality	None recorded			

*GRADE (Grades of Recommendation, Assessment, Development and Evaluation) certainty of evidence scoring was low given lack of prospective or randomised studies. CI = confidence interval; ESD = endoscopic stapler-assisted diverticulotomy; ELD = endoscopic carbon dioxide laser diverticulotomy; OR = odds ratio

to grade the certainty of evidence. For all articles, initial level of certainty rating was 'low', as established for retrospective non-randomised studies of interventions. The level of certainty was not upgraded; although no significant evidence of inconsistency, indirectness, imprecision or publication bias was present, bias because of confounding has already been discussed and was thought to favour endoscopic stapler-assisted diverticulotomy treatment groups.

Discussion

Previous review articles have reported a greater prevalence of pharyngeal perforation but a more complete diverticulotomy and fewer recurrences when comparing endoscopic carbon dioxide laser diverticulotomy to endoscopic stapler-assisted diverticulotomy.[2] Our findings concur with those of the 2014 review by Parker and Misono, demonstrating no significant difference after meta-analysis between endoscopic stapler-assisted diverticulotomy and endoscopic carbon dioxide laser diverticulotomy in terms of pharyngeal perforation or need for re-operation. Two larger studies included in our review described a technique of reducing residual party-wall by sawing off the redundant tip of the staple device; this may have had an impact on re-operation rate in the endoscopic stapler-assisted diverticulotomy group, but an effect is difficult to measure. Our findings of one case of vocal fold paralysis in each pooled treatment group do not support the hypothesis that endoscopic stapler-assisted diverticulotomy reduces the risk of thermal damage to the recurrent laryngeal nerve compared with endoscopic carbon dioxide laser diverticulotomy.[22]

Our conclusions are limited by the level of evidence available. No prospective or randomised studies comparing endoscopic stapler-assisted diverticulotomy and endoscopic carbon dioxide laser diverticulotomy exist; only non-randomised studies of interventions could be included. Baseline confounding with regards to rationale for treatment selection existed. Bias resulting from discrepancy in post-intervention regimen was likely to have favoured the endoscopic stapler-assisted diverticulotomy group because detection and reporting of complications in a more strictly monitored endoscopic carbon dioxide laser diverticulotomy group would be expected to be greater.

During the review process, significant heterogeneity in reporting of Zenker's diverticulum recurrence and length of follow up was encountered. In some studies, recurrence was defined by persistence of symptoms on follow-up questionnaire[14,17] or a long-term change in diet.[15] In the remaining studies, definition of Zenker's diverticulum recurrence was not stated. Although there exists potential for recurrences to be missed because of a reluctance to seek follow up or pursue revision surgery, re-operation rate was widely reported and uniformly defined, so was used as a surrogate measure of Zenker's diverticulum recurrence.

Dysphagia is among the most important outcome measures when comparing treatments for Zenker's diverticulum but could not be reliably assessed in our review. Three studies in our review measured dysphagia scores: the Modified Dysphagia Scale from Stoeckli and Schmid (2002),[23] a modified Functional Oral Intake Scale originally validated in stroke patients[24] and the validated Eating Assessment Tool-10[25] from Belafsky *et al*. Because of heterogeneity between scores, pooled and meta-analysis of dysphagia scoring was not possible. Other outcomes with variable levels of reporting included post-operative length of stay and rate of abandonment of procedure; it would be useful for these outcomes to be assessed in future research.

It is accepted that while the risk of recurrence is reduced when Zenker's diverticulum is managed with open surgery and cricopharyngeal myotomy,[26] endoscopic treatment with laser or stapler diverticulotomy represents a more practical treatment for many patients, especially for older adults and those with co-morbidities. The results of our systematic review suggest that both approaches are similar in terms of safety and efficacy. Our review did not compare the cost of each technique; while it is accepted that the equipment required for endoscopic carbon dioxide laser diverticulotomy requires a greater initial outlay, many departments already have access to and experience with laser operating.

Conclusion

This systematic review included nine retrospective, non-randomised studies of interventions comparing outcomes of endoscopic stapler-assisted diverticulotomy to endoscopic carbon dioxide laser diverticulotomy and was able to include more up-to-date data and exclude poor-quality studies when compared with previous reviews. Meta-analysis found no difference between treatment groups in terms of pharyngeal perforation, re-operation or major post-operative complication. Although our method of analysis and the lack of prospective data mean that we are unable to confirm or refute our experimental hypothesis, endoscopic stapler-assisted diverticulotomy and endoscopic carbon dioxide laser diverticulotomy appear comparable in terms of safety and efficacy. The authors advocate the discussion of risks and benefits of open treatment of Zenker's diverticulum with suitable young and healthy patients but recognise that both endoscopic stapler-assisted

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diverticulotomy and endoscopic carbon dioxide laser diverticulotomy are safe alternatives.

In order to establish which endoscopic treatment is superior, a well-designed, prospective, randomised, controlled study is needed. Ideally this should be carried out by a multidisciplinary team. As well as reporting rate of pharyngeal perforation, recurrence or need for re-operation, outcomes should include subjective and objective assessment of swallow (for example dynamic imaging), validated dysphagia scores and patient-reported outcome measures.

Competing interests. None declared

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