



# Systematic review and meta-analysis on the treatment of diffuse esophageal spasm

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## Summary

**Background** Diffuse esophageal spasm is a rare motility disorder and although diagnosis has improved over the years, optimal treatment remains controversial. The aim of this study was to determine the success rates of alternative treatments for diffuse esophageal spasm.

**Methods** MEDLINE, EMBASE, and the Cochrane Library were searched for studies which reported treatment outcomes in patients with diffuse esophageal spasm. The primary outcome measure was success rate. Secondary outcome measures were morbidity and mortality.

**Results** Ten observational studies involving 101 patients (35 male, 66 female, median age 61 years) with diffuse esophageal spasm treated with nifedipine ( $n=24$ ), botulinum toxin ( $n=41$ ), and surgery ( $n=46$ ) were analyzed. At a median follow-up of 8 months, the overall success rates for nifedipine, botulinum toxin, and surgery were 42.74% (95% c.i. [42.68–42.79],  $p<0.00001$ ), 74.39% (95% c.i. [74.27–74.52],  $p<0.00001$ ), and 95.74% (95% c.i. [95.69–95.80],  $p<0.00001$ ), respectively. Morbidity after surgery was 2% and no operative deaths were reported.

**Conclusion** Surgery appears to be safe and the most successful treatment. The less invasive medical and botulinum toxin therapies provide short-term symptom relief.

**Keywords** Nifedipine · Treatment · Diffuse esophageal spasm · Myotomy · Botulinum toxin

## Introduction

Diffuse esophageal spasm (DES) is a rare condition with an annual incidence of 0.2/100,000, occurring in some 3–5% of esophageal motility disorder (OMD) cases [1, 2]. It is more likely to occur in patients over the age of 50 years and should be considered as a differential diagnosis in elderly patients presenting with unexplained esophageal symptoms [3]. Although dysphagia and chest pain are the two most common presenting symptoms, DES can often resemble gastroesophageal reflux disease (GERD) [3]. In keeping with its rarity in the general population, such symptom heterogeneity renders DES a challenging condition to diagnose, commonly resulting in diagnostic delay [3], and esophageal manometry represents the diagnostic investigation of choice [4, 5]. However, this is not a first-line investigation but indicated after routine investigations have ruled out other causes of chest and esophageal symptoms [4–6]. DES is defined manometrically by the distal latency (DL), which refers to the frequency of premature contractions [7]. If premature contractions occur in >20% of swallows and the integrated relaxation pressure is normal, then a diagnosis of DES can be made [7].

With the introduction of the Chicago Classification in 2008 and improvements in investigations, diagnostic certainty has improved [8]. Yet, although treatment options have developed over the past 5 years, controversies remain regarding the optimum treatment [9, 10]. The aim of this study was to determine the success rates of different treatment options for patients with DES. The primary outcome measure was the relative treatment success rate and secondary outcome

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measures were treatment-related morbidity and mortality.

## Materials and methods

### *Data source and search strategy*

A systematic review of current published literature was performed in accordance with the Meta-Analysis of Observational Studies and Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Register, Cochrane Library, were the databases selected to carry out the systematic search. A sensitive search strategy that combined the exploded thesaurus term for diffuse esophageal spasm or free-text terms in the title or abstract for “diffuse [o]esophageal spasm\*” was developed. A preliminary literature search had been performed to identify what treatment options for DES had been investigated in the literature to date. The options found were included through exploded thesaurus terms or free-text terms in the search. The results were limited to human trials published in English language. No date limit was set to include as many trials as possible.

### *Study selection*

**Inclusion criteria:** Studies reporting treatment outcomes in patients with DES were included.

**Exclusion criteria:** For meta-analysis of data, a given treatment required two or more studies. Therefore, if only one study could be found on the given treatment, it was disregarded. Reviews and case reports were excluded.

### *Data extraction*

Data Extraction and quality assessment data was extracted by H. Vercoe, M. Mulla, D. Chan using an agreed protocol and any discrepancies were discussed with all authors to reach a consensus. The following information were extracted from each study: treatment option assessed, first author, article title, year of publication, country of origin, total number of patients, number of DES patients, age, gender, presenting symptoms, prior treatment, mean follow-up, definition of success, number of successes, duration of success, number of adverse events, morbidity, mortality. Authors were not contacted for incomplete data. The primary outcome measure was the rate of success for a given treatment. The definition of success varied depending on the outcome measures that were assessed in different papers. Secondary outcome measures included rate of adverse events, morbidity, and mortality, which were noted but not included in the meta-analysis calculations. Study quality was deter-

mined using the Newcastle–Ottawa scale, which examines patient selection methods, comparability of study groups, and assessment of outcome. A score of at least six stars from a maximum of nine was considered to indicate higher quality.

### *Data synthesis and statistical analysis*

The meta-analysis was performed in line with the recommendations from the Cochrane Collaboration and PRISMA guidelines using Review Manager 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Meta-analysis was used to pool study estimates of the outcome measures as detailed above. The pooled estimated outcomes were calculated using generic inverse variance random effects meta-analysis with standardized mean differences and 95% confidence intervals (c.i.) quoted. Where results showed that there was 0% or 100% success, a success rate of 0.01 or 0.99 was used in place of 0 or 1, respectively, in order to obtain an estimate of the overall success rate using Review Manager 5.3.

## Results

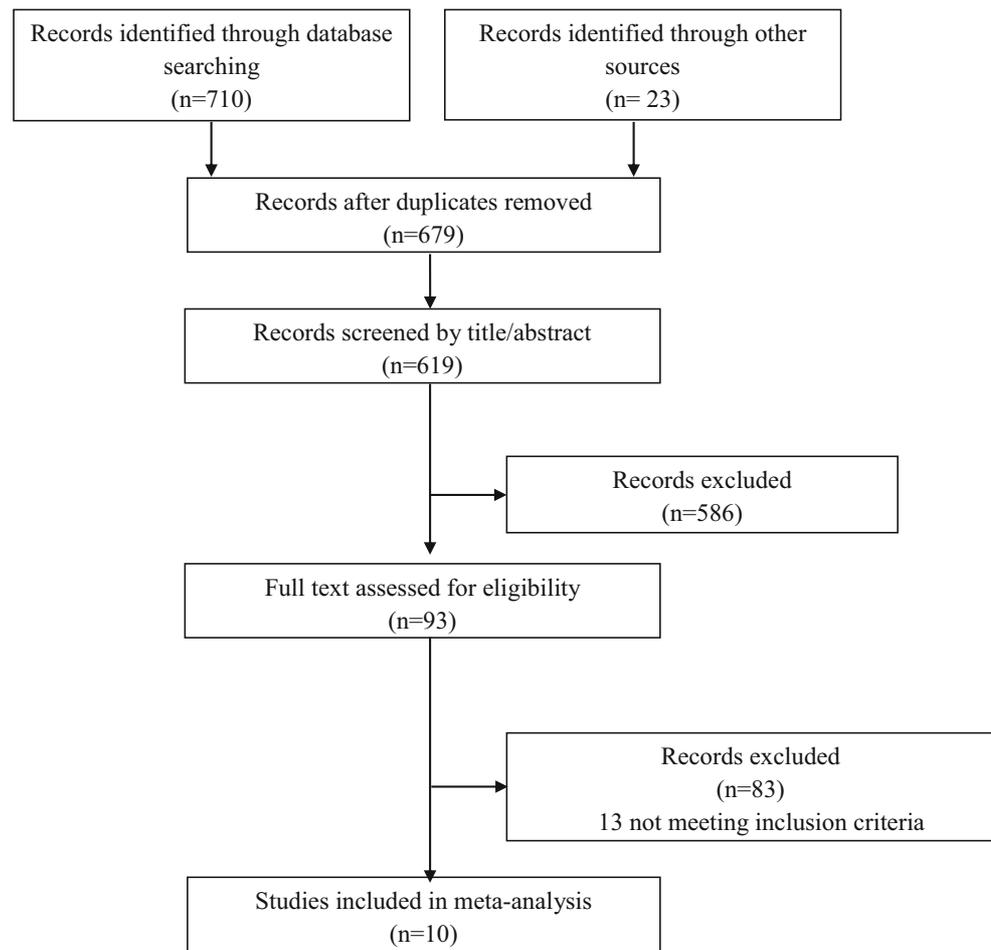
The literature search identified 179 citations through MEDLINE and 531 citations through EMBASE. There were no results in the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Register only had 13 results. After reviewing titles and abstracts and removing duplications, 96 articles were identified as being relevant. Of these, 10 studies fulfilled the inclusion criteria and were included in the meta-analysis ([11–20]; Fig. 1). Three focused on surgery [11–13], three focused on botulinum toxin [14–16], and four looked at the effect of nifedipine [17–20] as a treatment option for DES.

### *Study characteristics*

In total, 101 patients with DES were included in the meta-analysis, of whom 24 were treated with nifedipine, 41 with botulinum toxin, and 46 were treated surgically. The median age was 37, 63, and 66 years in the medical, botulinum toxin, and surgery groups respectively. The median duration of follow-up was 1.5, 12, and 24 months in the respective groups. The demographic data and study characteristics are summarized in Table 1.

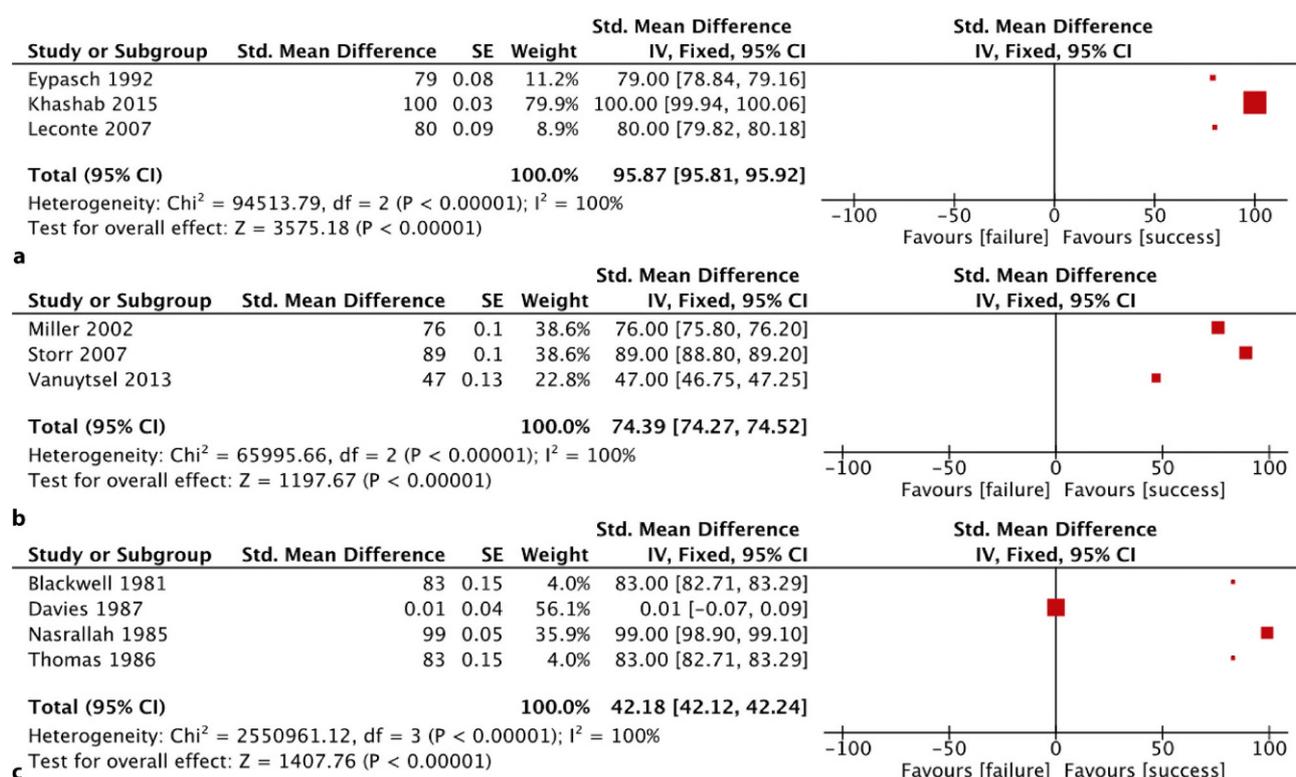
### *Characteristics of included studies*

All selected medical treatment studies examined the effectiveness of nifedipine. However, the objectives and methods differed between studies. For example, Davies et al. reported the long-term effects of nifedipine on DES, whereas Blackwell et al. reported the effectiveness of acute administration on symptom relief.

**Fig. 1** Identification process for eligible studies**Table 1** Characteristics of studies included in the meta-analysis

Author	Year	Country	Total	Age~	Male (n)	F/U~	NO^	Success definition	Number of successes
<i>Medical—nifedipine</i>									
Blackwell [17]	1981	Scotland	6	36	4	–	5	Reduction >2 mm Hg in LES pressure	5
Davies [18]	1987	UK	8	39	4	1.5	6	Significantly reduced pain severity and frequency score	0
Nasrallah [19]	1985	USA	4	–	–	1	6	Symptom improvement score >7 (0–10)	4
Thomas [20]	1986	USA	6	–	3	3	6	>50% reduction in symptom score, on scale 0–10	5
<i>Botulinum toxin</i>									
Miller [14]	2002	USA	17	61	4	24	6	≥50% reduction in chest pain score	13
Storr [15]	2001	Germany	9	71	3	6	7	Total symptom score of ≤3	8
Vanuytsel [16]	2013	Belgium	15	63	4	12	8	Modified Vantrappen criteria for achalasia	7
<i>Surgery</i>									
Eypasch [11]	1992	USA	17	–	–	24	6	Would patient have operation again?	15
Khashab [12]	2015	USA	9	71	6	8	7	Eckardt score of 0–3	9
Leconte [13]	2007	France	20	62	7	50	7	Eckardt score of 0 or 1	16

F/U Follow-up, NO Newcastle-Ottawa score, LES lower esophageal sphincter



**Fig. 2** Forest plots showing the meta-analysis and overall success rates for (a) surgery, (b) botulinum toxin, and (c) nifedipine therapy. SE standard error, Std standard

The surgical techniques also varied between selected studies. In the study by Eypasch et al., 15 patients had a long esophageal myotomy and 4 patients had a total esophagectomy with comparable results. Khashab et al. reported the effectiveness of per-oral endoscopic myotomy (POEM), and Leconte et al. conducted a trial examining extended myotomy effectiveness.

### Success rates

The success rates reported by the various studies on the different treatment approaches are shown in (Fig. 2).

### Medical

The overall pooled success rate of medical therapy was 42.74% (95% c.i. [42.68–42.79],  $p < 0.00001$ ). However, the percentage of successes varied from 100 to 0% between the four studies. Side effects from nifedipine such as headache, dizziness, and orthostatic hypotension occurred in 21% of medically treated patients.

### Botulinum toxin

Botulinum toxin injection had an overall pooled success rate of 74.39% (95% c.i. [74.27–74.52],  $p < 0.00001$ ). There were no adverse events and no increases in morbidity or mortality.

### Surgery

Surgery was the most effective treatment with an overall pooled success rate of 95.74% (95% c.i. [95.69–95.80],  $p < 0.00001$ ). There was an overall morbidity of 6% but no perioperative deaths.

The median duration of success for medical, botulinum toxin, and surgical treatment was 1.5, 6, and 8 months respectively.

### Heterogeneity

Heterogeneity was significant in all analyses ( $I^2 = 100\%$ ).

### Discussion

#### Surgery

This meta-analysis suggests that surgery is the most effective treatment for DES, which is in keeping with previous reports contending that surgery was more successful than conservative therapeutic options, including medication and/or pneumatic dilatation [21]. When compared with nifedipine, surgery was over 50% more effective, and when compared with botulinum toxin, over 20% more effective. Yet surgery is still considered a “last resort” for patients in whom conservative treatments have failed [22].

Whilst surgery is inevitably associated with inherent risk, evolving techniques such as per-oral endoscopic myotomy (POEM) have reduced morbidity and mortality with improved success rates [23, 24]. Several

case reports have demonstrated positive outcomes after POEM for DES, and have detailed its advantages [25–27]. Firstly, there is no limit to the length of myotomy that can be performed with a POEM procedure, which is one of the limitations of a Heller myotomy [26, 27]. Secondly, POEM preserves the esophago-gastric junction and longitudinal muscle layer of the esophagus, which may contribute to better success [25, 27].

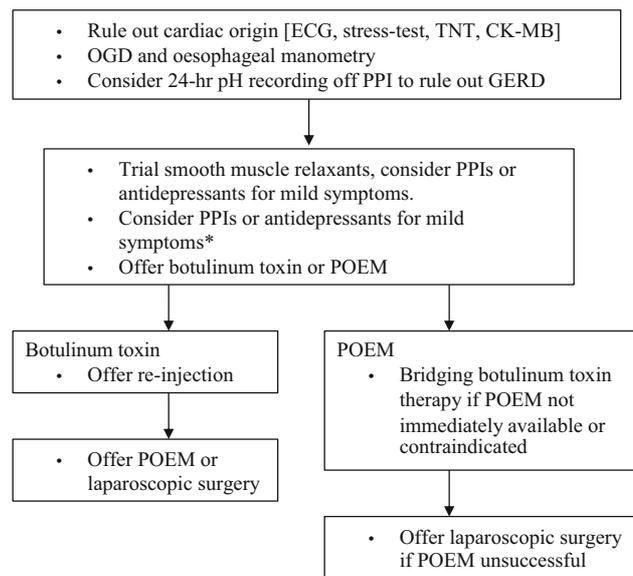
When comparing the surgical techniques used in the selected studies in this meta-analysis, POEM also appeared to be the most favorable. Khashab et al. performed POEM on all patients with 100% success, despite two adverse events [12]. In comparison, Eypasch and Leconte, who performed thoracoscopic long esophageal and extended myotomies, respectively, had less success [11, 13]. The international POEM survey (IPOEMS) reported that POEM was slightly less effective for treating DES than type I/II achalasia and other spastic esophageal motility disorders [28]. However, it reported that across all centers, Eckardt scores improved significantly and the overall efficacy for the POEM procedure was excellent [28].

### Botulinum toxin

The use of botulinum toxin injection also appeared to be reasonably effective, but its limitations were that its success was often short lived and repeated injections were required to maintain symptom control [14, 29]. Miller et al. demonstrated this: the mean duration of success was 7 months (range 1–18 months) and 47% of patients required a second injection [14]. Clearly this isn't the case for all patients; symptomatic relief can last beyond 7 months and re-injection isn't always necessary [30]. In 1996, Miller et al. reported that a third of patients had a good long-term response without the need for re-injection [29]. Should re-injection be necessary, success rates are lower but still acceptable [31]. Collectively, there is evidence to show long-term therapy with botulinum toxin is possible with or without re-injection [31]. Botulinum toxin is useful as a bridging therapy, which makes use of its short-term effectiveness [31], and is often used when other more permanent therapies are not immediately available or are contraindicated [31].

### Medical therapy

The success of nifedipine varied significantly between the included studies with relatively low overall success. Blackwell et al. reported how nifedipine can help relieve acute symptoms with some success, whilst Davies et al. reported the effectiveness of long-term treatment and found no response [17, 18]. Despite the lack of response in Davies' study, nifedipine was found to be effective at relieving acute chest pain [18]. From these two studies, it was contended that nifedipine could have more benefit if used for short-



**Fig. 3** Flow diagram of treatment pathway for patients with DES. \*Neither PPIs nor antidepressants have been explored as a treatment option in this paper but should be considered if pain could be GERD related or have a psychological component. (Adapted from a diagram by Bashashati et al. [31])

term relief as required. Side effects are common with nifedipine, which may also contribute to poor success and the short duration of success. It affected the doses administered in Thomas' study and prevented long-term use, despite the promising symptom scores [20].

Only studies which used nifedipine met the inclusion criteria of this meta-analysis. Other smaller studies have reported similarly poor results with alternative medication. Drenth et al. reported the effectiveness of Diltiazem, an alternative calcium channel blocker with fewer side effects, but found no statistical significance when compared with placebo [32]. Nevertheless, 75 and 67% of patients reported symptom improvement regarding chest pain and dysphagia index, respectively [32]. Drenth suggested that treatment should be considered on an individual patient basis given that response varies [32]. The high incidence of GERD in patients with DES (49%) also implies that acid suppression therapy may be helpful in relieving symptoms in many [3], but to date, there is no evidence supporting acid suppression therapy in treating DES and further research work is required before that recommendation could be made.

The Bashashati et al. review summarized a therapeutic approach for patients with DES [31]. A simple three-step pathway was proposed with medical, botulinum toxin therapy, and surgery considered consecutively. This meta-analysis would suggest surgery, in particular POEM, should be considered earlier (Fig. 3).

### Strengths

The strengths of this study are the relatively large numbers of patients with DES included. Due to the rarity of this condition, there are no randomized controlled trials comparing the various treatment options, and all studies had 20 or fewer patients, making direct comparison of individual studies difficult. This meta-analysis allows the quantitative comparison of the various treatment options for DES, thus informing clinicians and patients alike about the expected success and morbidity rates.

### Limitations

This study has a number of inherent potential limitations. Meta-analysis of retrospective cohort studies is regrettably sensitive to confounding and selection bias. The number of studies available for meta-analysis was limited, especially in the medical group. The most recent study was published in 1987 and numbers across all the selected studies were low. Success was defined in various ways. Most studies used questionnaires to determine the severity and change of symptoms to define the success of the intervention. Only one study objectively measured the reduction of lower esophageal sphincter (LES) pressure [17]. As a result, heterogeneity was significant across the analyses. Moreover, data exclusive to patients with DES were not extractable from some studies which included patients with other esophageal motility disorders alongside DES.

### Conclusion

In conclusion, surgery is safe and the most successful treatment option for patients diagnosed with DES. Less invasive treatment in the form of medical and botulinum toxin therapy provide short-term symptom relief.

**Author Contribution** All authors contributed to the conception or design of the work and/or the acquisition, analysis, and interpretation of data. Drafts were revised critically for important intellectual content and the final version approved by all. All agree to be accountable for all aspects of the work.

**Conflict of interest** H. Vercoe, M. Mulla, W.G. Lewis, A. Foliaki, and D.S.Y. Chan declare that they have no competing interests.

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