Laparoscopic Heller Myotomy Versus Endoscopic Balloon Dilatation for the Treatment of Achalasia

A Network Meta-Analysis

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Objective: Comparison of short- and long-term effects after laparoscopic Heller myotomy (LHM) and endoscopic balloon dilation (EBD) considering the need for retreatment.

Background: Previously published studies have indicated that LHM is the most effective treatment for Achalasia. In contrast to that a recent randomized trial found EBD equivalent to LHM 2 years after initial treatment.

Methods: A search in Medline, PubMed, and Cochrane Central Register of Controlled Trials was conducted for prospective studies on interventional achalasia therapy with predefined exclusion criteria. Data on success rates after the initial and repeated treatment were extracted. An adjusted network meta-analysis and meta-regression analysis was used, combined with a head-to-head comparison, for follow-up at 12, 24, and 60 months.

Results: Sixteen studies including results of 590 LHM and EBD patients were identified. Odds ratio (OR) was 2.20 at 12 months (95% confidence interval: 1.18–4.09; $P = 0.01$); 5.06 at 24 months (2.61–9.80; $P < 0.00001$) and 29.83 at 60 months (3.96–224.68; $P = 0.001$). LHM was also significantly superior for all time points when therapy included re-treatments [OR = 4.83 (1.87–12.50), 19.61 (5.34–71.95), and 17.90 (2.17–147.98); $P \leq 0.01$ for all comparisons) Complication rates were not significantly different. Meta-regression analysis showed that amount of dilations had a significant impact on treatment effects ($P = 0.009$). Every dilation (up to 3) improved treatment effect by 11.9% (2.8%–21.8%).

Conclusions: In this network meta-analysis, LHM demonstrated superior short- and long-term efficacy and should be considered first-line treatment of esophageal achalasia.

Keywords: achalasia, economic cost, endoscopy, esophagus, health, idiopathic achalasia, laparoscopic surgery, meta-analysis, motility disorders, network meta-analysis, review, surgery

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Achalasia is a rare esophageal motility disorder caused by degeneration of the myenteric plexus, resulting in esophageal dysmotility and incomplete lower esophageal sphincter relaxation. The disease is likely caused by a virus-induced autoimmune response, but this is still debated.[1] The incidence in the Western world is 1/100 000.[2] The diagnosis is based on typical clinical symptoms (dysphagia for solids and liquids, retrosternal pain, and weight loss), and on endoscopy, manometry, and barium swallow findings.[2–4] Treatment can be pharmacological, endoscopic, or surgical. Pharmacological treatment is only marginally effective and is reserved for patients with mild symptoms or who refuse other treatments.[4] Currently, treatments include endoscopic balloon dilation (EBD) and endoscopic botulinum toxin injection (EBTI). EBTI has been shown to be inferior compared to EBD at relieving symptoms, and to be less durable.[4–6]

Surgical myotomy was first described in 1914, and, since 1991, it is mainly performed laparoscopically.[7–9] Several studies and a large meta-analysis have indicated that laparoscopic Heller myotomy (LHM) is the most effective treatment for achalasia.[3,4,10] However, a recent large prospective randomized controlled trial (RCT) comparing EBD and LHM has challenged this view.[11] This study found similar success rates for EBD and LHM 2 years after initial treatment. However, the number of EBD interventions per patient was notably higher than other studies.[3,11] The purpose of this meta-analysis is to determine which treatment is most effective at relieving symptoms and to further clarify the impact of retreatments for patients with achalasia.

METHODS

This meta-analysis was registered in the international register of systematic reviews (PROSPERO) (CRD42012002071).[12]

Search Strategy and Trial Selection

A prospective search of Medline, PubMed, and Cochrane Central Register of Controlled Trials was performed to identify relevant publications. The search keyword was "Esophageal Achalasia." Subsequently, the search was limited by the terms "Human," "Clinical Trial," and publication language "English." Publications from 1975 through October 2011 were considered for review (Fig. 1). Final results were imported into Review Manager software (RevMan, Version 5.0.24; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). For further selection, prospectively defined exclusion criteria were used. The primary exclusion criteria eliminated animal studies, in vitro studies, case reports, prospective nonrandomized studies (see later), retrospective studies, studies with less than 3-month follow-up or with fewer than 10 patients, abstracts only, and publications in a language other than English.

To obtain indirect evidence by adjusted network meta-analysis, relative evidence is needed (LHM vs X; EBD vs X). Therefore, success rates were compared with those of either EBTI or open Heller myotomy (OHM). Direct evidence was achieved from head-to-head comparisons (LHM vs EBD). Figure 2 gives an example of how such an analysis is constructed.[13] Because the quantity of RCTs was found to be insufficient for an adjusted network meta-analysis with long-term follow-up, the exclusion criteria were amended to include prospective nonrandomized trials (PNRTs) comparing either LHM or EBD with the above-mentioned benchmark procedures.

Data Extraction

Baseline data was extracted. This included type of study, sample size, and mode of comparison. Additionally patient based baseline data was sex, duration of symptoms, and length of follow-up period.

Efficacy

Clinical success rates were defined according to the assessment of the investigators conducting the studies (eg, clinical scores, manometric findings, or clinical interviews with review of symptoms).

1. Clinical success rates after initial treatment were extracted. Because treatment protocols differed from study to study (eg, up to 5 planned treatment sessions for EBD), we defined initial therapy as "Initial treatment or series of initial treatments as defined per study protocol before relapse." For LHM, the initial surgery always represented the defined "initial treatment." For EBD, the first treatment or series of treatments (ie, 1–3 EBD treatments as defined in the individual study protocol) was defined as "initial treatment." The data comprising the initial treatment protocol were extracted. The number of procedures was noted for both LHM and EBD. In addition, the number of EBD treatments prior to LHM and type of antireflux procedure were counted. Relevant parameters for EBD such as duration of dilation and balloon diameter were included in the analysis.

A meta-regression analysis was used to estimate effects of the number of procedures, dilation time, and balloon diameter used on success rates for EBD. To investigate the effects of the variables, a Poisson Model with repeated measures was performed.

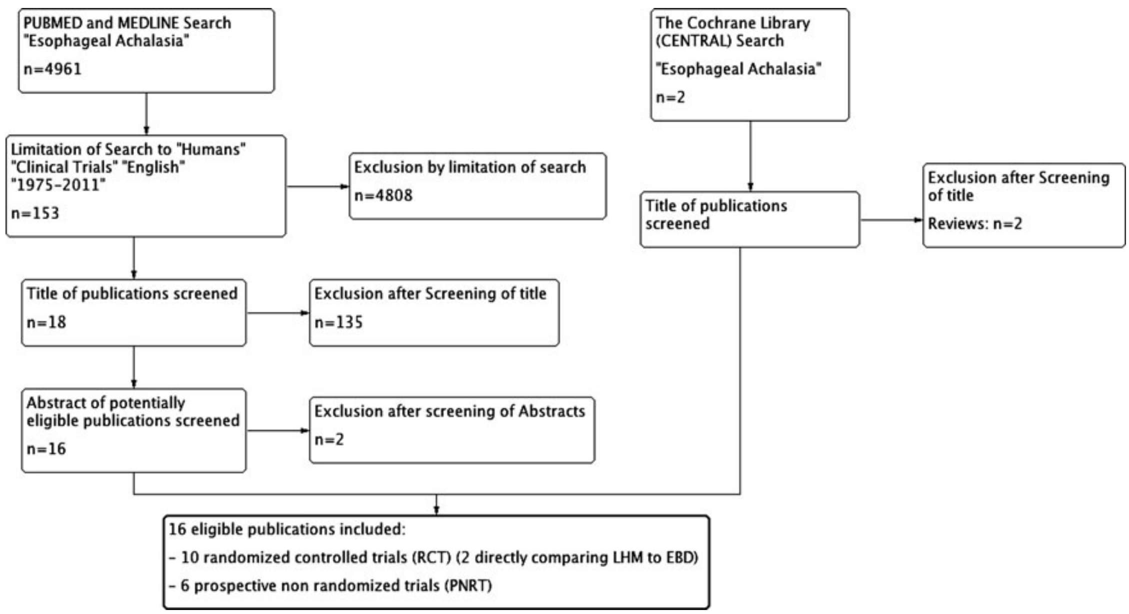

FIGURE 1. Flow diagram detailing the search strategy.

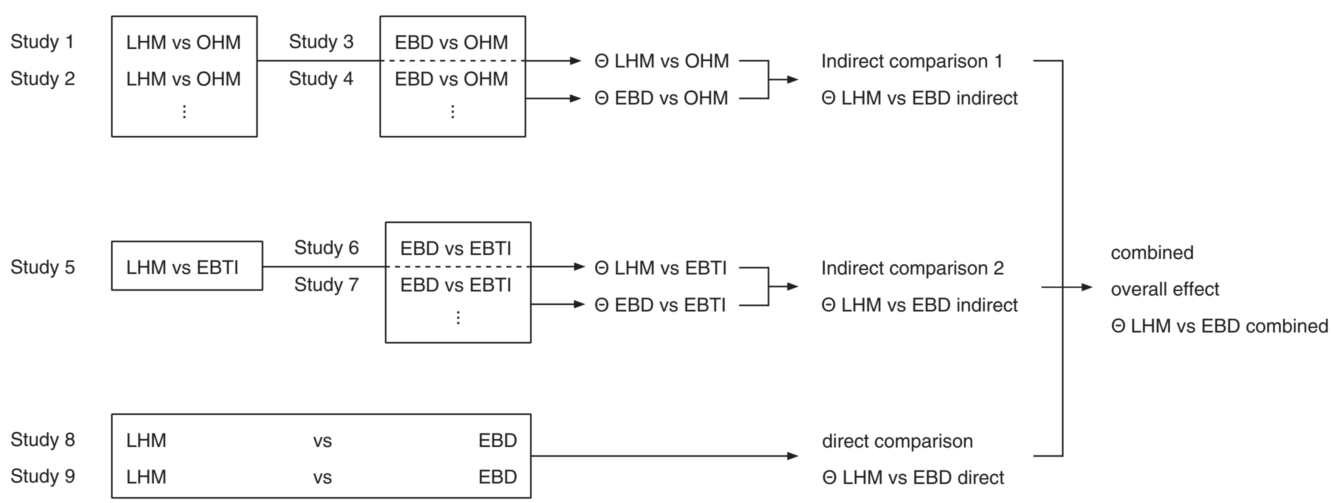

FIGURE 2. Example of a network meta-analysis combined with a head-to-head comparison. Modified from Schöttker et al.[13]

2. The number of re-treatments was extracted. Re-treatment was prospectively defined as any treatment that was necessary beyond the prospectively determined initial treatment protocol because of symptom relapse. Success rates that took into account additional balloon dilations were calculated to examine the overall effect including redilations. Any number of additional balloon dilations was allowed because most publications did not specify the exact number of redilations for individual patients. In this analysis additional surgical interventions were not included because in many protocols LHM was regarded as the last line of treatment and therefore subsequent data were not available after surgery.

Because not all trials measured success rates at the same time points, 12, 24, and 60 months were predefined. Relapse events before any time point were extracted for both groups (initial treatment and treatment including redilations) and counted at the next time point of data analysis in the particular studies.

Complications

Complications were classified according to the Clavien-Dindo grade. The classification is based on the treatment that is required as a result of the complication or the effect of the complication (eg, death).[14,15] The classification is detailed in Table 1. Perforations during LHM that were sutured immediately were not graded as complications using this scale unless there was a postoperative consequence, but they were noted separately. The rate of conversion to open Heller myotomy during LHM and the incidence of posttreatment gastroesophageal reflux disease (GERD) requiring antisecretory medication were also included in the analysis.

TABLE 1. Definitions of the Clavien-Dindo Score to Grade Postinterventional Complications

Full Scale Grading System	
Grades	*Definition*
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III:	Requiring surgical, endoscopic, or radiological intervention.
Grade III-a:	Intervention not under general anesthesia.
Grade III-b:	Intervention under general anesthesia.
Grade IV:	Life-threatening complication (including CNS complications)* requiring IC/ICU management.
Grade IV-a:	Single-organ dysfunction (including dialysis).
Grade IV-b:	Multiorgan dysfunction.
Grade V:	Death of a patient.
Suffix "d"	If the patients suffer from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding transient ischemic attacks.

IC indicates intermediate care; ICU, intensive care unit.

Assessment of Validity

To assess validity of evidence for this analysis, homogeneity and similarity were explored.[16,17] Homogeneity of all meta-analyses forming the basis of our analysis was calculated with MIX 1.7 (MIX Version 1.7; BiostatXL, Sunnyvale). An analysis was deemed homogenous if the P value of the Cochran Q was greater than 0.1. To explore similarity, a risk of bias analysis of all studies included was performed using the "Risk of bias" tool within the RevMan software. In addition to the "Risk of Bias" study, quality was assessed with the Jadad and the Colditz Score.[18–20] Age was noted and a meta-regression analysis of possible moderators of treatment effect was conducted (see earlier).

Statistical Analysis

Data were collected in a database (Microsoft Excel 2008 for Mac; Version 12.2.8, Microsoft Corporation, Redmond). Continuous variables were expressed as means (standard deviation). Direct and indirect evidence was calculated using success rates after initial and additional treatments.

Two RCTs that directly compared LHM with EBD were available for a meta-analysis that would provide direct evidence. For a combined analysis, data on outcomes of initial and additional treatments were only available for a maximum follow-up of 12 months.[10,11] For direct evidence, a fixed-effect meta-analysis using the RevMan software was employed.

Indirect evidence was obtained from an adjusted network meta-analysis,[17,21,22] with EBTI and OHM being used as benchmarks (Fig. 2). MIX 1.7 and SAS (SAS System, Version 9.2; SAS Institute Inc, Cary) were used to calculate relative treatment effects for the indirect comparison.

Combination of the indirect and direct comparisons was performed with a fixed-effect model in RevMan.[22] The relative treatment effect calculated by direct and indirect comparisons are presented as odds ratios (ORs) with 95% confidence intervals. Success rates at all separate time points were regarded as independent. Agreement was calculated using the Cohen kappa in the R software (R Software Version 2.15.3; R Foundation for Statistical Computing).[23,24] The χ^2 test was used to approximate differences in complication rates. A $P < 0.05$ was considered statistically significant.

RESULTS

Study Inclusions

The Medline, PubMed, and Cochrane Central Register of Controlled Trials search for "Esophageal Achalasia" yielded 4963 publications. After limiting the search according to the exclusion criteria listed previously, 153 publications remained that were then screened by title. Subsequently, 18 abstracts were obtained and after the abstracts were reviewed, 16 trials investigating results from 907 patients were included in this analysis. Out of these studies, only 2 directly compared LHM with EBD.[10,11] Nine RCTs and 5 PNRTs compared LHM or EBD with either EBTI or OHM[5,6,25–36] (Tables 2–4). LHM, EBD, EBTI, and OHM procedures were performed in 235, 355, 210, and 107 patients, respectively. For this network analysis, only the treatment effects in patients treated with EBD and LHM (n = 590) were calculated. The baseline data on parameters of the initial treatment protocol for each study can be found in Tables 5 and 6.

Analysis of data points determined by 2 independent reviewers (M.B.S. and D.v.R.) regarding success rates resulted in a mean Cohen kappa coefficient reflecting an almost perfect agreement ($\kappa = 0.842$).

Assessment of Validity

The calculation of heterogeneity of 18 meta-analyses with and without additional treatment, which formed the basis for the network

TABLE 2. Baseline Data on All Studies Comparing Laparoscopic Heller Myotomy (LHM) to a Benchmark

Reference	Year	Study Type	Jadad Score (0–5)	Colditz Score (0–7)	Comparison Mode	Sample Size (N)	Sex (M/F)	Duration of Symptoms, Median (Range)	Median Follow up, Median (Range)
Collard et al	1996	PC	1	3	LHM	12	10/2	NA	NA
					OHM	8	2/6		
Douard et al	2004	PC	1	5	LHM	52	24/28	35.5 (4–288) mo	50 (12–102) mo
					OHM	30	14/16	29 (5–684) mo	53 (12–92) mo
Zaninotto et al	2004	RCT	2	6	LHM	40	18/22	24 (2–240) mo	23 (12–34) mo
					EBTI	40	18/22	18 (2–240) mo	

TABLE 3. Baseline Data on All Studies Comparing EBD With a Benchmark

Reference	Year	Study Type	Jadad Score (0–5)	Colditz Score (0–7)	Comparison Mode	Sample Size (N)	Sex (M/F)	Duration of Symptoms, Mean ± SD or Median (Range)	Median (Follow-up), Mean ± SD or Median (Range)
Allescher et al	2001	PC	1	6	EBD	23	NA	NA	48.56 ± 15.19
					EBTI	14			45.21 ± 14.27 mo
Annese et al	1996	RCT	3	6	EBD	8	3/5	53.2 (12–80) mo	16 (6–24) mo
					EBTI	8	4/4	33.7 (6–154) mo	
Bansal et al	2003	RCT	4	7	EBD	18	12/6	33.6 ± 10.2 mo	16.3 (3–23) mo
					EBTI	16	7/9	23.5 ± 5.1 mo	14.8 (2–24) mo
Csendes et al	1989	RCT	3	7	EBD	39	16/23	NA	58 (24–144) mo
					OHM	42	20/22		62 (26–156) mo
Gockel et al	2004	PC	1	5	EBD	48	28/20	3.34 (0.1–15)*	10 (2.8–17.5)*
					OHM	27	19/8	3.07 (0.1–20)*	8.23 (4.6–13.1)*
Ghoshal et al	2001	RCT	3	7	EBD	10	5/5	42.6 ± 49.2 mo	8.31±2.95
					EBTI	7	5/2	107 ± 102.0 mo	7.91±3.88
Mikaeli et al	2001	RCT	3	7	EBD	19	10/9	5.9 ± 7.7†	NA
					EBTI	20	9/11	6.9 ± 6.2†	
Muehldorfer et al	1999	RCT	2	5	EBD	12	14/10	NA	30 mo
					EBTI	12			
Prakash et al	1999	PC	1	4	EBD	26	18/8	6.0 ± 2.3†	37.2 ± 6
					EBTI	42	24/18	5.7 ± 1.0†	18 ± 2.4
Vaezi et al	1999	RCT	4	6	EBD	24‡	17/7	NA	NA
					EBTI	24§	14/10		
Zhu et al	2009	RCT	3	6	EBD	28	12/16	3.5 (1.2–4.3) yrs	NA
					EBTI	29	13/16		
					EBD + EBTI¶	30	17/13		

*Weighted calculation.
†No scale of measurement provided.
‡4 patients preexcluded from analysis.
§2 patients preexcluded from analysis.
¶Not part of our analysis.
NA indicates not available.

TABLE 4. Baseline Data on All Studies Directly Comparing LHM with EBD

Reference	Year	Study Type	Jadad Score (0–5)	Colditz Score (0–7)	Comparison Mode	Sample Size (N)	Sex (M/F)	Duration of Symptoms (Months) Mean ± SD or Median (Range)	Median (Range) Follow-up (Months)
Boeckxstaens et al	2011	RCT	2	5	LHM	106	57/49	NA	43 (40–47) mo
					EBD	108*	60/35 (13 NA)		
Kostic et al	2007	RCT	3	7	LHM	25	11/14	62.5 ± 14.9 (6–240) mo	NA
					EBD	26	13/12	107 ± 102.0 (1–240) mo	

*13 patients preexcluded from analysis.

TABLE 5. Initial Treatment Protocol for LHM (Laparoscopic Heller Myotomy)

		Initial Treatment Protocol		
Reference	Year	No. Procedures	EBD Prior to Operation (n)	Antireflux Procedure
Boeckxstaens et al	2011	1	None	Dor
Collard et al	1996	1	6	Dor
Douard et al	2004	1	28	Dor
Kostic et al	2007	1	None	Toupet
Zaninotto et al	2004	1	None	Dor or Nissen

TABLE 6. Initial Treatment Protocol for EBD

		Initial Treatment Protocol		
Reference	Year	No. Procedures	Duration of Dilation, s	Diameter Balloon, mm
Allescher et al	2001	1	120	35
Annese et al	1996	1–3*	120	30–35
Bansal et al	2003	1	180	40
Boeckxstaens et al	2011	2–3†	60s	30–35
Csendes et al	1989	2	10–20	40
Gockel et al	2004	1	120	NA
Ghoshal et al	2001	1	60	NA
Mikaeli et al	2001	1	30	30
Muehldorfer et al	1999	2	180	40
Prakash et al	1999	1	30	30–35
Vaezi et al	1999	1	60	30
Zhu et al	2009	1	90	30

*Second and third dilation with the 35-mm balloon was allowed if the patients tolerated the procedure.
†Fourth dilation after recurrence of symptoms during first 2 years of follow-up optional.

meta-analyses, showed to be homogenous with a median Cochran Q of 0.37 (Range: 0.01–8.53; all analyses $P > 0.1$) at 12, 24, and 60 months.

Risk of bias analysis showed overall a low risk of bias for all studies (Supplemental Data File 1, available at http://links.lww.com/SLA/A462). Analysis of study quality yielded a mean Jadad Score of 2.31 (1.08) (Range: 1–4) and a Colditz score of 5.75 (1.18) (Range: 3–7). Mean ages across all treatment options were 41.3 (5.3), 45.6 (6.0), 50.8 (7.5), and 46.2 (10.7) for LHM, EBD, EBTI, and OHM, respectively.

Success Rates After Initial Treatment

Direct evidence comparing LHM with EBD was available for a maximum follow-up of 12 months and is shown in a Forest plot (Fig. 3). After initial treatment, success rates after LHM were significantly higher than after EBD [OR = 3.77 (1.61, 8.84), $P = 0.002$, Fig. 3].

In the indirect comparison, success rates did not differ significantly at 12 months. However, at 24 and 60 months, a rising treatment effect favoring LHM is apparent (Table 7). Indirect comparison combined with head-to-head comparison shows significantly better results for LHM compared to EBD after 12 months [OR = 2.20 (1.18, 4.09), $P = 0.01$] (Fig. 4). Consistently, LHM significantly outperformed EBD at 24 months in the analysis [OR = 4.53 (2.33, 8.82), $P < 0.001$] (Fig. 5). No direct evidence is available for the 60-month time point. Indirect comparison demonstrates an increasing treatment effect favoring LHM with an OR of 29.83 (3.96, 224.68), $P = 0.001$ (Table 7). Results of the indirect and combined analyses and patient numbers available for follow-up at respective time points is shown in Table 7. The raw data of success rates are available in the Supplemental Data File 2, available at http://links.lww.com/SLA/A463.

Parameters Influencing EBD Outcomes

Relevant parameters such as number of EBD procedures, dilation time, and diameter of the dilation balloon were assessed (Table 6). Meta-regression showed a significant effect of the number of dilations used in the initial treatment protocol ($P = 0.009$) on the subsequent treatment success rate. Starting with 1 dilation, minimally constituting the initial treatment protocol every subsequent dilation (up to 3) improved the treatment effect by 11.9% (2.8%, 21.8%) ($P = 0.009$). The duration of dilation ($P = 0.054$) and the diameter of the balloon ($P = 0.88$) showed no statistically significant effect on success rates. However, extending the balloon dilation for 10 seconds (up to 180 seconds) yielded a 2.0% (−0.1%, 4.2%) increase in success rates.

Retreatment

Among the 235 LHM patients, 18 additional procedures (all balloon dilations) were required to treat persistent or recurrent symptoms. Among the 355 EBD patients, additional procedures for treatment of relapse of symptoms were required in 153 cases—these consisted of 110 balloon redilations, 3 EBTIs, 3 botulinum toxin injections followed by pneumatic dilation, 36 surgical myotomies, and 1 esophagectomy (Table 8).

Success Rates Including Redilations

When outcomes including all redilations were evaluated, comparing LHM directly with EBD after 12 months, LHM was associated with a significantly higher success rate [OR = 14.62 (1.85, 115.33) $P = 0.01$; Fig. 6]. In the indirect comparison, LHM outperformed EBD at all time points (Table 9). Treatment effects of indirect evidence combined with head-to-head comparison at 12 and 24 months were highly significant favoring LHM [OR = 4.83 (1.87, 12.50) $P = 0.001$ and OR = 19.61 (5.34, 71.95) $P < 0.001$; respectively; Figs. 7, 8]. Consequently, the indirect comparison at 60 months showed higher success rates following LHM (OR = 17.90 (2.17, 147.98) $P = 0.007$]. Detailed results are presented in Table 7 and raw data of success rates are available in the Supplemental Data File 3, available at http://links.lww.com/SLA/A464.

Procedure-Related Complications

Complications were recorded as early complications in the majority of studies. Evidence of late complications was not available in the published literature.

No mortalities or severe complications (Grade 4 + 5) were reported for either LHM or EBD. Using the Clavien-Dindo classification, investigators reported 2 grade 1 complications, both occurring after LHM. One patient developed a brachial plexitis (Parsonage-Turner syndrome) and another patient had urinary retention (compared with zero after EBD, $P = 0.309$). Grade 2 complications were found in 2 LHM patients (1 deep vein thrombosis and 1 conservatively treated fistula) and 3 EBD patients (3 conservatively treated perforations) ($P = 0.994$). No Grade 3a complications were reported. One patient had to undergo reoperation after LHM because of bleeding at a trocar site (Grade 3b), and 10 EBD patients had to undergo salvage surgery because of perforations ($P = 0.073$). The reported complications are summarized in Table 10.

Independently from the complication scores, 16 perforations (6.8%) were reported during LHM and were sutured laparoscopically.

Study or Subgroup	EBD Events	EBD Total	LHM Events	LHM Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Boeckxstaens 2011	17	85	7	98	86.9%	3.25 [1.28, 8.28]
Kostic 2007	6	26	1	25	13.1%	7.20 [0.80, 64.89]
Total (95% CI)		**111**		**123**	**100.0%**	**3.77 [1.61, 8.84]**
Total events	23		8			

Heterogeneity: $Chi^2 = 0.43$, df = 1 (P = 0.51); $I^2 = 0\%$
Test for overall effect: Z = 3.05 (P = 0.002)

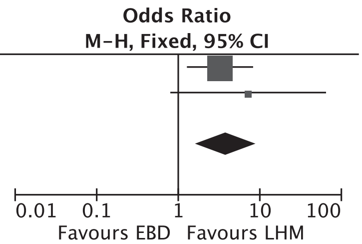

FIGURE 3. Forest plot after 12 months of direct comparison: Initial treatment effect. . Seventeen patients lost to follow-up or discontinued the study after 12 months in the publication by Boeckxstaens et al. M-H indicates Mantel-Haenszel.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Boeckxstaens 2011	1.1787	0.47686	44.2%	3.25 [1.28, 8.28]
Kostic 2007	1.9741	1.12174	8.0%	7.20 [0.80, 64.89]
X vs. EBTI	−0.82098	0.5319	35.5%	0.44 [0.16, 1.25]
X vs. OHM	3.2414	0.90278	12.3%	25.57 [4.36, 150.03]
Total (95% CI)			**100.0%**	**2.20 [1.18, 4.09]**

Heterogeneity: $Chi^2 = 18.33$, df = 3 (P = 0.0004); $I^2 = 84\%$
Test for overall effect: Z = 2.48 (P = 0.01)

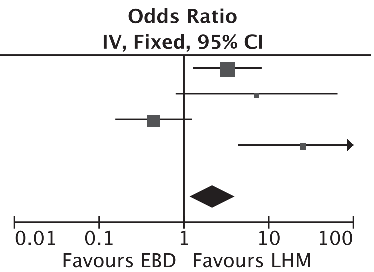

FIGURE 4. Forest plot after 12 months of the combined comparison: Initial treatment effect.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Direkt Boeckxstaens	1.2305	0.4118	68.1%	3.42 [1.53, 7.67]
X vs. EBTI	1.38879	0.7516	20.4%	4.01 [0.92, 17.49]
X vs. OHM	3.3955	1.0043	11.5%	29.83 [4.17, 213.55]
Total (95% CI)			**100.0%**	**4.53 [2.33, 8.82]**

Heterogeneity: $Chi^2 = 4.01$, df = 2 (P = 0.13); $I^2 = 50\%$
Test for overall effect: Z = 4.45 (P < 0.00001)

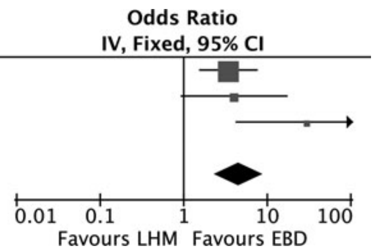

FIGURE 5. Forest plot after 24 months of the combined comparison: initial treatment effect.

TABLE 7. Summary of Treatment Effects After Initial Treatment, Number of Patients Available for Follow-up, and Level of Significance, From the Indirect and Combined Comparisons

Time, mo	Patients (N)	Indirect Treatment Effect, Odds Ratio (95% Confidence Interval); *P*	Combined Treatment Effect, Odds Ratio (95% Confidence Interval); *P*
12	895	1.25 (0.51–3.08); 0.62	2.20 (1.18–4.09); 0.01
24	707	8.24 (2.53–26.81); 0.0005	4.53 (2.33, 8.82); < 0.00001
60	256	29.83 (3.96–224.68); 0.001	No data from direct comparison available

TABLE 8. Amount of Retreatment Procedures After Relapse Following Initial LHM and EBD

	LHM (n)	EBD (n)
Overall	18	153
Redilations	18	110
Myotomy		36
Other interventions		3 botulinum toxin injections 3 botulinum toxin injections + pneumatic dilation 1 esophagectomy

Four operations (1.7%) had to be converted to an open procedure. Out of these, 3 conversions were due to an epiphrenic perforation and 1 was not specified.

Antireflux Procedures and Gastroesophageal Reflux Disease

In the LHM studies, all (100%) patients received an antireflux procedure. LHM was supplemented with 170 Dor (72.34%) and 25 Toupet (10.64%) fundoplications, and 40 (17.02%) patients received either a Nissen or a Dor fundoplication.[28] After LHM with antireflux procedure, 28 of 235 patients (11.86%) developed symptomatic GERD.

TABLE 9. Summary of Treatment Effects After Additional Treatment, Number of Patients Available for Follow-up, and Level of Significance, From the Indirect and Combined Comparisons

Time, mo	Patients, N	Indirect Treatment Effect, Odds Ratio (95% Confidence Interval); *P*	Combined Treatment Effect, Odds Ratio (95% Confidence Interval); *P*
12	895	3.59 (1.23–10.48); 0.02	4.83 (1.87–12.50); 0.001
24	707	20.66 (4.82–88.57); < 0.00001	19.61 (5.34–71.95); < 0.00001
60	256	17.90 (2.17–147.98); 0.0074	No data from direct comparison available

Study or Subgroup	EBD Events	EBD Total	LHM Events	LHM Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Boeckxstaens 2011	6	85	0	98	51.4%	16.11 [0.89, 290.27]
Kostic 2007	5	26	0	25	48.6%	13.05 [0.68, 249.61]
Total (95% CI)		**111**		**123**	**100.0%**	**14.62 [1.85, 115.33]**
Total events	11		0			

Heterogeneity: $Chi^2 = 0.01$, df = 1 ($P = 0.92$); $I^2 = 0\%$
Test for overall effect: Z = 2.55 ($P = 0.01$)

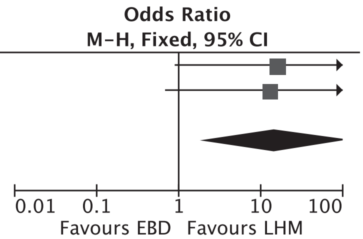

FIGURE 6. Forest plot after 12 months of direct comparison including additional redilations effect. Seventeen patients lost to follow-up or discontinued the study after 12 moths in the publication by Boeckxstaens et al.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Direkt Boeckxstaens	2.7794	1.4753	10.8%	16.11 [0.89, 290.31]
Direkt Kostic	2.5688	1.5058	10.4%	13.05 [0.68, 249.66]
X vs. EBTI	0.3646	0.6845	50.2%	1.44 [0.38, 5.51]
X vs. OHM	2.8848	0.9075	28.6%	17.90 [3.02, 106.00]
Total (95% CI)			**100.0%**	**4.83 [1.87, 12.50]**

Heterogeneity: $Chi^2 = 6.31$, df = 3 ($P = 0.10$); $I^2 = 52\%$
Test for overall effect: Z = 3.25 ($P = 0.001$)

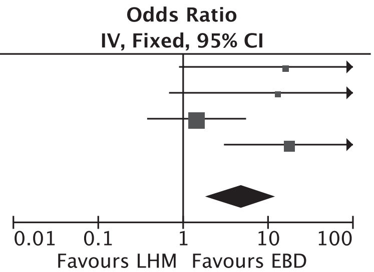

FIGURE 7. Forest plot after 12 months of the combined comparison including additional re-dilations effect.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Direkt Boeckxstaens	2.7688	1.4754	20.2%	15.94 [0.88, 287.30]
X vs. EBTI	3.0856	1.1731	32.0%	21.88 [2.20, 218.07]
X vs. OHM	2.9902	0.9592	47.8%	19.89 [3.03, 130.35]
Total (95% CI)			**100.0%**	**19.61 [5.34, 71.95]**

Heterogeneity: $Chi^2 = 0.03$, df = 2 ($P = 0.99$); $I^2 = 0\%$
Test for overall effect: Z = 4.49 ($P < 0.00001$)

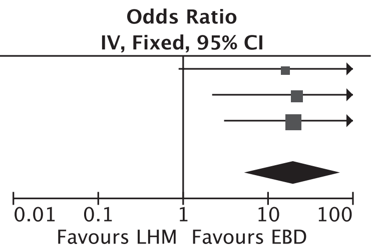

FIGURE 8. Forest plot after 24 months of the combined comparison including additional redilations effect.

DISCUSSION

Achalsia is currently treated with either EBD or LHM.[3,4] Previous reviews and meta-analyses have suggested that surgical myotomy is the most effective therapy.[3,4] Moreover, initial endoscopic therapy can increase the rate of treatment failure or complications for subsequent LHM.[37] Recent evidence from a randomized controlled study comparing LHM with EBD has challenged this view by demonstrating equivalent results for both treatments at 2 years. However, this study employed a more extensive EBD protocol compared to previous trials, allowing for up to 5 dilations within the first 6 months before considering a relapse of symptoms as a treatment failure. To determine the effects of repeated initial treatments and/or retreatment, the comparative efficacy of both therapies using defined end points and treatment sequences was analyzed by using a network meta-analysis.

Indeed, a meta-analysis of multiple RCTs would yield the most reliable results comparing the 2 treatment strategies. However, to date, only 2 RCTs directly comparing LHM and EBD have been published. Given the lack of such studies in the current literature, a network analysis can be used to compensate for the paucity of comparative RCTs.[38] Sixteen RCTs and PNRTs including 590 patients treated with LHM or EBD were analyzed. Tests for heterogeneity showed that studies were homogenous at all time points. "Risk of bias" analysis showed overall a low risk of bias (Supplemental Data File 1, available at http://links.lww.com/SLA/A462). Outcomes consistently demonstrate LHM to have significantly better short- and long-term success rates compared with EBD. LHM is superior to EBD after both initial and repeated treatments in the case of relapse. Only indirect comparison at 12 months after initial treatment showed no significant

TABLE 10. All Reported Complications in Every Study and Summary for LHM and EBD on the Clavien-Dindo Grading System. Additional Information on Minor Perforations

	Year	Grade 1	Grade 2	Grade 3a	Grade 3b	Grade 4a	Grade 4b	Grade 5	Minor Perforations	
EBD										
Allescher et al	2001	—	—	—	—	-	-	-	-	
Annese et al	1996	-	-	-	-	-	-	-	-	
Bansal et al	2003	-	-	-	2 Perforations	-	-	-	-	
Boeckxstaens et al	2011	-	2 Perforations	-	2 Perforations	-	-	-	-	
Csendes et al	1989	-	-	-	2 Perforations	-	-	-	-	
Ghoshal et al	2001	-	-	-	-	-	-	-	-	
Gockel et al	2004	-	1 Perforations	-	-	-	-	-	-	
Kostic et al	2007	-	-	-	2 Perforations	-	-	-	-	
Mikaeli et al	2001	-	-	-	-	-	-	-	-	
Muehldorfer et al	1999	-	-	-	-	-	-	-	-	
Prakash et al	1999	-	-	-	-	-	-	-	-	
Vaezi et al	1999	-	-	-	2 Perforations	-	-	-	-	
Zhu et al	2009	-	-	-		-	-	-	-	
LHM										
Zaninotto et al	2004	-	-	-	1 Bleeding	-	-	-	-	
Collard et al	1996	1 Personage turner syndrome	-	-	-	-	-	-	-	
Douard et al	2004	1 Urinary retention	1 Esophageal fistula, 1 deep venous thrombosis	-	-	-	-	-	3 Perforations	
Boeckxstaens et al	2011	-	-	-	-	-	-	-	13 Perforations	
Kostic et al	2007	-	-	-	-	-	-	-	-	
Intervention										
LHM		2 (0.85%)	2 (0.85%)	-	1 (0.43%)	-	-	-	16 (6.81%)	5 (2.13%)
EBD		-	3 (0.85%)	-	10 (2.82%)	-	-	-	-	13 (3.66%)
P		0.309	0.994	-	0.073	-	-	-	-	0.414

difference in success rates. In detail as seen in Figure 4, EBD outperformed LHM in comparison with EBTI at 12 months of follow-up after initial treatment. Because EBTI was studied in older patients than LHM, the relative treatment effect of LHM versus EBTI may have been underestimated. Results of EBTI have been reported to be better in the elderly people.[39] However, through combining direct and indirect evidence, the best available estimation of the real treatment effect is obtained.

Results are consistent with previous meta-analyses, such as the one published by Campos et al in which treatment effects at 12 and 36 months were measured. However, this meta-analysis did include studies published up to 2006 and, therefore, no data from the recent RCT.[11] Despite this difference, the ORs in this previous meta-analysis are almost the same as those found in our analysis (Table 7; Fig. 3).[3] In the meta-analysis by Wang et al,[4] the relative treatment effect directly after intervention was also significantly better for LHM (relative risk = 1.48, $P = 0.001$). This study, however, does not report follow-up periods. Patients undergoing LHM seem to need significantly less retreatments than EBD patients. It is common practice for many gastroenterologists to perform several EBDs to treat achalasia and then to advise surgery if symptoms relapse or if dilation with a 40-mm diameter balloon is not sufficient.[1,40]

Meta-regression analysis shows that additional dilations (up to 3) have a significant effect on the treatment success. Every additional dilatation improves EBD outcomes by 12%. This is consistent with clinical observations and explains the comparatively high success rates obtained in the recent prospective multicenter RCT.[11] Similarly the longer duration of dilation times showed a trend toward impacting treatment effects of after EBD. Nevertheless this did not reach statistical significance ($P = 0.054$). An additional 10 seconds of dilation time improved outcomes by 2% (up to max 180 seconds). This should be considered for dilatation protocols in the clinical setting. The diameter of the balloon utilized was not associated with improved outcomes. Considering the high perforation rate of 31% published in a RCT[11] when the study group was using a 35-mm balloon for initial treatment in therapy naïve patients, it seems clearly advisable not to go beyond 30 mm for initial EBD treatments.

Perforations are the most common complication after LHM or EBD. When compared with the study of Campos et al,[3] complication rates after LHM were lower in the present analysis (2.13% vs 6.3%. However, the applied Clavien-Dindo grading that was used in this analysis does not rate any perforations that are managed intraoperatively without any consequences for the patient as a complication. Boeckxstaens et al[11] rated these perforations as complications and hence found a significantly higher complication rate (12%). Procedure-related complications after EBD in our study were in the range of those found in previous studies. Interestingly, no reports of bleeding or aspiration during EBD can be found in the published literature. A closer look revealed that less severe complications (grades 1 and 2) are similar for LHM and EBD. This occurs because EBD perforations that are managed conservatively are considered to be grade 2 complications. However, complications leading to salvage surgery with general anesthesia occur more often after EBD, but this difference did not reach statistical significance ($P = 0.07$). Two publications removed patients with perforations after EBD from the analysis and therefore complication rates after EBD may have been underestimated.[11,27]

Reflux esophagitis can be a consequence of LHM or EBD. For prevention of reflux, an antireflux procedure was added in all studies after LHM. Reflux rates in the available studies were mostly defined clinically, by a score, or by a standardized 24-h pH-metry. LHM with fundoplication was associated with proton pump inhibitors dependent reflux rates of 12%.

Boeckstaens et al assessed reflux after EBD by endoscopy and 24-h pH-metry, but not clinically. Outcomes were comparable to LHM in this analysis. However, GERD data after EBD is reported too sparsely for a valid meta-analysis at present. Postprocedural GERD after EBD treatment remains an important topic to be assessed in future studies.[11]

High-resolution manometry allows for a more precise classification of achalasia and can classify subtypes, which possibly helps to better direct treatment strategies.[41] All subtypes show an impaired lower esophageal sphincter relaxation. Type 1 (“classic achalasia”) shows only minimal pressurization in the tubular esophagus, type 2 shows residual esophageal compression but no propulsive peristalsis, and type 3 shows high pan esophageal pressurization.

Depending on achalasia subtypes varying results have been reported, but LHM remains the most effective treatment amongst EBD and EBTI after the first intervention for all achalasia subtypes.[42,43] However, to date, no RCTs compare different treatment strategies based on high-resolution manometry. Future prospective studies should take this into account to establish treatment recommendations based on disease subtypes. Especially in light of new techniques such as POEM (peroral endoscopic myotomy), a more nuanced evaluation of treatment effects should be employed to find the most effective and minimally invasive treatment.[44,45]

Overall LHM achieves better outcomes and less need for retreatment. However, costs for LHM can initially be higher than for EBD.[46,47] Nevertheless, in late follow-up, after 5 and 10 years, incremental costs between EBD and LHM decrease by 25%. Considering the early onset of achalasia in most cases, the decrease of incremental costs lead to equalization of costs at some point in the very late follow-up, but sufficient data are not available at present stage.[46]

CONCLUSIONS

This study demonstrates that, in the first 5 years of follow-up, LHM is a more effective treatment for achalasia than EBD. EBD requires a greater number of initial treatment sessions, re-treatments, and salvage surgery for complications. Even when multiple treatments are used as part of the initial treatment protocol or in the case of recurrent symptoms, LHM remains a more effective long-term treatment approach. In light of these results, LHM should be considered first-line treatment for esophageal achalasia.

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to the conception and design of the study; interpretation of the data; provided critical revision of the manuscript; provided final approval of the version to be published. D.v.R. contributed substantially to the conception and design of the study, acquisition, analysis and interpretation of the data; drafting and revision of the manuscript; provided final approval of the version to be published.

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