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The comparisons of different therapeutic modalities for idiopathic achalasia

A systematic review and network meta-analysis

Sz-Iuan Shiu, MD[a,b,c], Chung-Hsin Chang, MD[a], Yu-Kang Tu, PhD[d,e,f], Chung-Wang Ko, MD[a,*]

Abstract

Background : Current guidelines recommend per-oral endoscopic myotomy (POEM) and laparoscopic Heller's myotomy (LHM) as first-line treatment of idiopathic achalasia, but the optimum choice between different endoscopic and surgical modalities remains inconclusive. We conducted a network meta-analysis to compare the efficacy of 8 treatments for idiopathic achalasia.

Materials and methods : Three major bibliographic databases were reviewed for enrollment of randomized controlled trials between January 2000 and June 2021. We included adults with idiopathic achalasia and compared two or more of eight interventions including botulinum toxin injection (BTI), pneumatic dilation (PD), BTI + PD, LHM without fundoplication, LHM followed with Dor or Toupet fundoplication, and POEM using either the anterior or posterior approach. Our focus was on clinical success rate, postsurgical acid reflux, and moderate-to-severe adverse events.

Results : Twenty-four studies involved a total of 1987 participants for analysis. When compared with PD, POEM with anterior approach, POEM with posterior approach, LHM + Toupet, and LHM + Dor were all significantly superior to the other regimens in short-term efficacy, with POEM with anterior approach and LHM + Dor showing better improvement in mid-term efficacy. BTI showed a significantly lower efficacy than PD in both periods. Regarding safety, only LHM without fundoplication was significantly associated with higher acid reflux than PD, while LHM + Toupet, LHM without fundoplication, and LHM + Dor showed a non-significant increase in moderate-to-severe adverse events.

Conclusions : For idiopathic achalasia, we suggest that POEM with an anterior or posterior approach and LHM with Dor or Toupet fundoplication be initially recommended. On the contrary, both LHM without fundoplication and BTI are not recommended as definitive therapy.

Abbreviations: BTI = botulinum toxin injection, BTI + PD = combined therapy of botulinum toxin injection plus pneumatic dilation, CI = confidence interval, dPD = double sessions of PD, GERD = gastroesophageal reflux disease, IQR = interquartile ranges, LES = lower esophageal sphincter, LHM = laparoscopic Heller's myotomy, LHM + Dor = laparoscopic Heller's myotomy with Dor fundoplication, LHM + Toupet = laparoscopic Heller's myotomy with Toupet fundoplication, NMA = network meta-analyses, ORs = odds ratios, PD = pneumatic dilation, POEM = per-oral endoscopic myotomy, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses, RCTs = randomised controlled trials, sPD = single session of PD.

Keywords: idiopathic achalasia, laparoscopic Heller's myotomy, network meta-analysis, per-oral endoscopic myotomy, pneumatic dilation

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[a] *Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan,* [b] *Department of Critical Care Medicine, Taichung Veterans General Hospital, Taichung, Taiwan,* [c] *Evidence-based Practice and Policymaking Committee, Taichung Veterans General Hospital, Taichung, Taiwan,* [d] *Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan,* [e] *Department of Medical Research, National Taiwan University Hospital, National Taiwan University, Taipei, Taiwan,* [f] *Department of Dentistry, National Taiwan University Hospital and School of Dentistry, National Taiwan University, Taipei, Taiwan.*

[*] *Correspondence: Chung-Wang Ko, No. 1650 Taiwan Boulevard Sect. 4, Taichung 40705, Taiwan (e-mail: cwko@vghtc.gov.tw).*

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1. Introduction

Idiopathic achalasia is an esophageal motility disorder typified by insufficient relaxation of the lower esophageal sphincter (LES) in the setting of absent peristalsis.[1] Although annual incidence is rare, ranging from 1.07 to 1.99 per 100,000 people,[2–4] as well as a reported prevalence of 10.8 to 27.1/100,000[2,4] due to the chronicity of achalasia, the disorder is associated with an increased overall mortality and higher incidence of esophageal cancer globally.[4,5] Therefore, successful management of achalasia in clinical practice is an important issue surrounding disease prevention.

The pathophysiology of achalasia is related to the functional loss of myenteric plexus ganglion cells in the distal esophagus and LES,[6] where alleviating the contractility of LES to achieve adequate esophageal emptying is the primary goal of achalasia treatment. In 1970, Witzel produced the prototype of through-the-scope balloon dilation, with Shimi et al[7] performing the first laparoscopic Heller's myotomy (LHM) in 1991. Two types of partial fundoplication are usually employed to prevent postoperative gastroesophageal reflux disease (GERD): anterior Dor fundoplication and posterior Toupet fundoplication. Per-oral endoscopic myotomy (POEM) was introduced and standardized by Inoue et al[8] and has been in use since 2010. It can be performed either anteriorly at the 1 to 2 o'clock position or posteriorly at the 5 to 6 o'clock location.[9]

Network meta-analyses (NMA), also known as mixed treatment comparisons, simultaneously compares multiple treatment comparators by using direct and indirect comparisons with a preservation of randomization in individual trials.[10–12] Recently, two NMAs[13,14] aimed at determining the optimal achalasia treatment amongst pneumatic dilation (PD), LHM, and POEM were conducted, and the results differed from each other. Aiolfi et al reported that POEM was associated with better dysphagia remission and higher GERD events when compared with PD and LHM based upon 19 studies involving 14 observational cohort and 5 randomised controlled trials (RCTs). Mundre et al enrolled subjects from 9 RCTs and found that both POEM and LHM were superior to PD in terms of efficacy, while there was no significance with regards to either adverse events or GERD after intervention. Meanwhile, the optimum achalasia treatment regarding different endoscopic and surgical modalities remains elusive despite intensive investigations.

In the present study, we conducted an NMA to compare the relative efficacy and safety of achalasia treatments amongst 8 endoscopic and surgical modalities for patients with idiopathic achalasia. Furthermore, we performed a subgroup analysis to determine the priority of procedures for addressing achalasia in treatment-naïve patients, as well as in patients receiving PD when divided into either single or double sessions.

2. Materials and methods

2.1. Search strategy and selection criteria

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement,[15] as well as the PRISMA extension guideline[16] for NMA (see Table S1, Supplemental Digital Content, http://links.lww.com/MD/G738, which illustrates PRISMA extension checklist). We searched various electronic databases including PubMed, Embase, and the Cochrane Central Register of Controlled Trials without any language restrictions, and also performed a manual literature search of bibliographies in retrieved articles and published reviews from eligible publications. Studies in abstract form were also enrolled for inclusion. A detailed description of the search strategies is provided in Table S2, Supplemental Digital Content, http://links.lww.com/MD/G739, which illustrates electronic database searching strategy. Because minimally invasive Heller's myotomy is considered the gold standard surgical procedure for symptomatic achalasia and has safely and effectively been in use since the 1990s,[17] we restricted the inclusion of articles to only those published between January 1, 2000, and June 4, 2021.

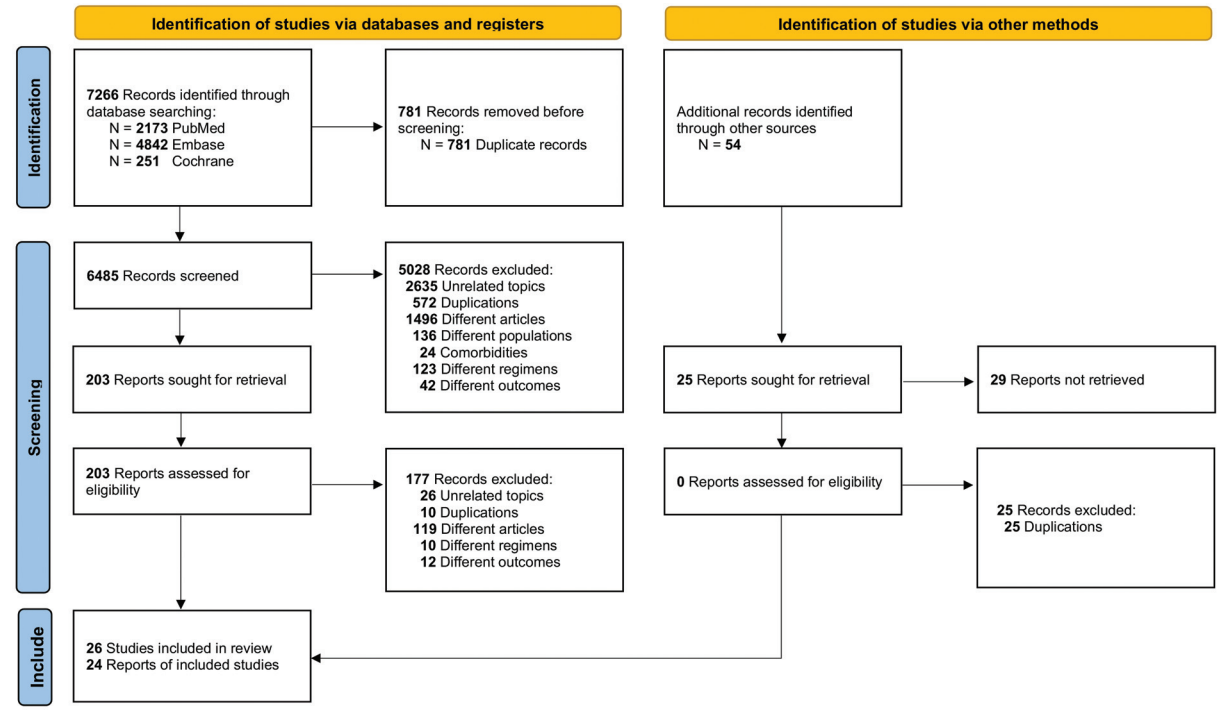
We included RCTs with active-controlled designs that evaluated the efficacy and safety of interventions in adults (aged $\geq$ 18 years) with symptomatic and idiopathic achalasia which had been confirmed according to clinical backgrounds, as well as one or more typical diagnostic findings (barium swallow, upper gastrointestinal endoscopy, or manometry) with esophageal manometry as essential criteria. We included reports that compared two or more of eight interventions, including botulinum toxin injection (BTI), PD, combined therapy of BTI plus PD (BTI+PD), LHM without fundoplication, LHM followed with Dor or Toupet fundoplication, or POEM using either the anterior or posterior approach. Reports that involved pediatric patients, pregnant women, or patients with secondary causes to achalasia, gastrectomy, endoscopic submucosal dissection, malignancy (including gastric or non-gastric origins), and severe concurrent comorbidities were excluded.

2.2. Outcome measures

For the primary outcome, we determined the clinical success rate of intention to treat analysis at both short-term ($\leq$1 year) and mid-term (2–3 years) follow-up periods, after completion of interventions from the enrolled studies. We defined clinical success as there being no need for retreatment during follow-up, or any symptom remission on quantifiable outcomes scores, for example, the Eckardt score, Demeester grading of dysphagia, or the Vantrappen and Hellemans dysphagia score. For secondary outcomes, we analyzed the rate of abnormal gastroesophageal acid reflux through per-protocol analysis with a minimal duration of 6 months follow-up post treatment, as well as the moderate-to-severe adverse events immediately after treatments in order to investigate their therapeutic safety. Gastroesophageal acid reflux was considered abnormal based upon symptom-based questionnaires, and objective pH measurements. Moderate-to-severe adverse events were recorded if significant complications requiring prolonged hospitalization, or additional endoscopic or surgical procedures occurred. Ethical approval and informed consent from the participants were not necessary as there was no individual participant data involved.

2.3. Data extraction and quality assessment

Two investigators (S-IS and C-HC) first independently screened the titles and abstracts for eligibility, and then full texts were assessed to clarify the eligibility status of each article. All discrepancies were discussed and resolved in consultation with a third investigator (C-WK). Non-English articles were translated. We calculated the intention to treat or attempted to contact the corresponding author(s) if it was not indicated within the article. Two reviewers (S-IS and C-HC) extracted data independently, with the data then checked by a third investigator (C-WK). The



From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.

Figure 1. PRISMA 2020 flow diagram.

following variables were extracted: country of study, participants' characteristics, inclusion criteria, details of comparative interventions, and dichotomous outcome measurements.

We grouped endoscopic and surgical interventions into 8 groups, listed from the oldest to the newest: BTI, PD, BTI + PD, LHM without fundoplication, or LHM followed with Dor (LHM + Dor) or Toupet (LHM + Toupet) fundoplication, and POEM using either the anterior (Anterior POEM) or posterior (Posterior POEM) approach. Two investigators (S-IS and C-HC) evaluated the risk of bias of all studies independently and assessed the quality of the articles included in the analysis using version 2 of the Cochrane tool for assessing Risk of Bias in randomised trials (RoB 2.0 tool).[18,19] Disagreements were discussed until a consensus was reached, with a third investigator (C-WK) being consulted when necessary.

2.4. Data synthesis and statistical analysis

The NMA, which consisted of direct and indirect comparisons, was conducted under the frequentist model and generalized linear mixed models.[20] We undertook mixed treatment comparisons of NMA using a random-effect model, which was based upon the *mvmeta* command, with the restricted maximum likelihood approach applied in the Stata program (version 16; Stata, College Station, TX),[21] in order to investigate treatment efficacy and safety. The pooled odds ratios (ORs) and 95% confidence interval (CI) were reported for binary variables and for dichotomous variables of safety, where we noted zero events. No imputation for zero cell counts of 0.5 was performed.

Heterogeneity amongst the enrolled studies was evaluated by the τ statistic. Additionally, we evaluated any potential inconsistencies between direct and indirect evidence within the NMA using the design-by-treatment interaction model,[22] the loop-specific approach, and the side-splitting method.[23,24] Statistical significance was set at 5% for all analyses. We also calculated the probabilities of each treatment being at each rank for each intervention and outcome. We obtained a treatment hierarchy using both the surface under the cumulative ranking curve and mean ranks.[25] Comparison-adjusted funnel plots[26] and Egger's tests were used to examine potential small-study bias after treatments were placed in order from oldest to newest. In order to investigate of the source of heterogeneity, we conducted sensitivity analyses in which studies in abstract form, articles including unavailable medical history, Chagas' disease, per-protocol analysis, and trials with a <6-month follow-up period were all omitted.

2.5. Subgroup analysis

In addition, we performed subgroup analysis to determine the priority of procedures for treating achalasia in treatment-naïve patients during short-term and mid-term follow-up durations, as well as in patients receiving PD divided into either single or double sessions.

3. Results

After primary screening of the titles and abstracts, 203 full-text articles were assessed for eligibility (Fig. 1). Ultimately, we included 26 articles for qualitative analysis and 24 articles involving a total of 1987 participants for quantitative synthesis. Three of the included studies were subsequent investigations of previously published trials with only two reported interested outcomes,[27,28] along with another study[29] which didn't describe any detailed procedure for fundoplication after LHM.

3.1. Characteristics of the included studies

The methodology and characteristics of the study design and patients' outcomes are summarized in Tables S3, S4, and S5, Supplemental Digital Content, http://links.lww.com/MD/G870, http://links.lww.com/MD/G871, http://links.lww.com/MD/G872, which illustrates the characteristics of enrolled RCTs. Among these studies, sample sizes ranged from 34 to 241 (median 68), while the medians and interquartile ranges (IQRs) for age and percentage of male gender were 48.6 years (IQR, 44.0–50.9), and 48.3% (IQR, 45.6–54.6), respectively. Most studies were performed in the Americas and Europe (72.7%), with the remainder being from either Asian (22.7%) or African (4.6%) nations. Most trials enrolled treatment naïve patients (63.6%), where LHM + Dor (26.1%), PD (22.5%), and Anterior POEM (22.0%) were the most common interventions randomly assigned in our review, followed by Posterior POEM (12.7%), LHM + Toupet (7.2%), BTI (6.1%), BTI + PD (2.3%), and LHM without fundoplication (1.1%). The Cochrane Collaboration's Risk of Bias assessment is shown in Table S6, Supplemental Digital Content, http://links.lww.com/MD/G873, which illustrates the risk of bias for enrolled RCTs. High risk was common in overall bias because some studies did not describe both the allocation sequence method and randomization process thoroughly, or either the trial personnel or participants were aware of their medications during the blinding process. Non-adherence to intervention protocol and missing data without an analysis method to correct bias also influenced clinical outcomes. Taken together, the aforementioned procedural issues resulted in risk of bias regarding the domains of randomization, deviations from the intended interventions, as well as missing outcome data. Additionally, most of the included studies were not blind to outcome assessors where symptomatic scores might be influenced by awareness of the interventions, thus resulting in some concern regarding the domain of measurement surrounding the outcome.

3.2. Primary outcome: efficacy

The geometry for network comparisons regarding the short-term efficacy of achalasia treatments is shown in Figure 2, while the forest plot of NMA is shown in Figure 3. When compared with PD (reference regimen), Anterior POEM (OR 3.78, 95% CI: 1.93–738), Posterior POEM (OR 3.75, 95% CI: 1.47–9.54), LHM + Toupet (OR 3.69, 95% CI: 1.13–12.12), and LHM + Dor (OR 2.29, 95% CI: 1.50–3.49) all showed significantly greater efficacy and were at least twice as effective as the reference group with only BTI (OR 0.33, 95% CI: 0.17–0.63) showing significantly lower efficacy. The medians (IQRs) for short-term clinical successful rates (%) of Anterior POEM, Posterior POEM, LHM + Toupet, BTI + PD, LHM + Dor, PD, and BTI were 91.1 (IQR, 84.4–95.4), 92.1 (IQR, 87.0–93.0), 93.9 (IQR, 90.2–97.0), 85.4 (IQR, 84.4–86.5), 86.7 (IQR, 79.7–88.7), 66.35 (IQR, 56.0–77.7), and 53.3 (IQR, 37.5–60.0), respectively. Moreover, all of the above treatments showed a significantly higher efficacy when compared to BTI in indirect comparisons of NMA as summarized in Table 1.

As for mid-term efficacy of achalasia treatments, the geometric distribution and forest plot of NMA are reported in Figures S1A and S2A, Supplemental Digital Content, http://links.lww.com/MD/G704, http://links.lww.com/MD/G710. In brief, Anterior POEM and LHM + Dor offered a higher improvement than PD, at a statistical significance. We also performed subgroup analyses in treatment naïve individuals with short-term follow-up and mid-term follow-up durations (see Figures S1B–S1C, and S2B–S2C,

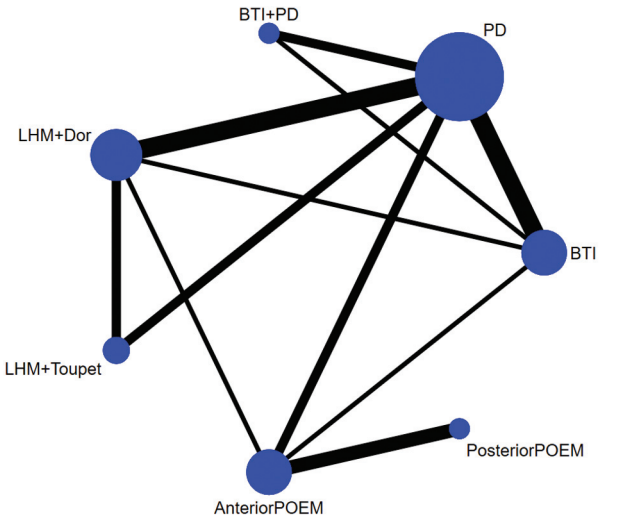


Figure 2. Network comparisons using geometry of different therapeutic modalities for achalasia (≤1-year follow-up period). BTI = botulinum toxin injection, LHM = laparoscopic Heller's myotomy, PD = pneumatic dilation, POEM = per-oral endoscopic myotomy.

Supplemental Digital Content, http://links.lww.com/MD/G705, http://links.lww.com/MD/G706, http://links.lww.com/MD/G711, http://links.lww.com/MD/G712, which displays network comparisons geometry and forest plot of short-term and mid-term efficacy in treatment naïve achalasia). In contrast to PD, Anterior POEM ranked first in the short-term follow-up group, followed by LHM + Toupet, and LHM + Dor at a significant difference. In treatment naïve individuals with mid-term outcome, only LHM + Toupet and Anterior POEM had better benefits with statistical significance in comparison with PD. Furthermore, a trend of higher efficacy in achalasia treatments was also noted among Anterior POEM, Posterior POEM, LHM + Toupet, BTI + single session of PD (sPD), and LHM + Dor when compared to double sessions of PD (dPD) (see Figures S1D and S2D, Supplemental Digital Content, http://links.lww.com/MD/G707, http://links.lww.com/MD/G713, which displays network comparisons geometry and forest plot of short-term efficacy when compared to dPD).

The League Table is shown in Tables S7A to S7D, Supplemental Digital Content, http://links.lww.com/MD/G744, http://links.lww.com/MD/G745, http://links.lww.com/MD/G746, http://links.lww.com/MD/G747, as well as the surface under the cumulative ranking curve probability in Figures S3A to S3E, Supplemental Digital Content, http://links.lww.com/MD/G716, http://links.lww.com/MD/G717, http://links.lww.com/MD/G718, http://links.lww.com/MD/G719, http://links.lww.com/MD/G720. Funnel plot revealed visual symmetry (see Figures S4A–S4E, Supplemental Digital Content, http://links.lww.com/MD/G723, http://links.lww.com/MD/G724, http://links.lww.com/MD/G725, http://links.lww.com/MD/G726, http://links.lww.com/MD/G727), and the Egger's test showed no significant publication bias (see Figures S5A–S5E, Supplemental Digital Content, http://links.lww.com/MD/G730, http://links.lww.com/MD/G731, http://links.lww.com/MD/G732, http://links.lww.com/MD/G733, http://links.lww.com/MD/G734). Simultaneously, we used several methods to assess inconsistency between direct and indirect evidence (see Tables S8–S10, Supplemental Digital Content, http://links.lww.com/MD/G750, http://links.lww.com/MD/G751, http://links.lww.com/MD/G752, which

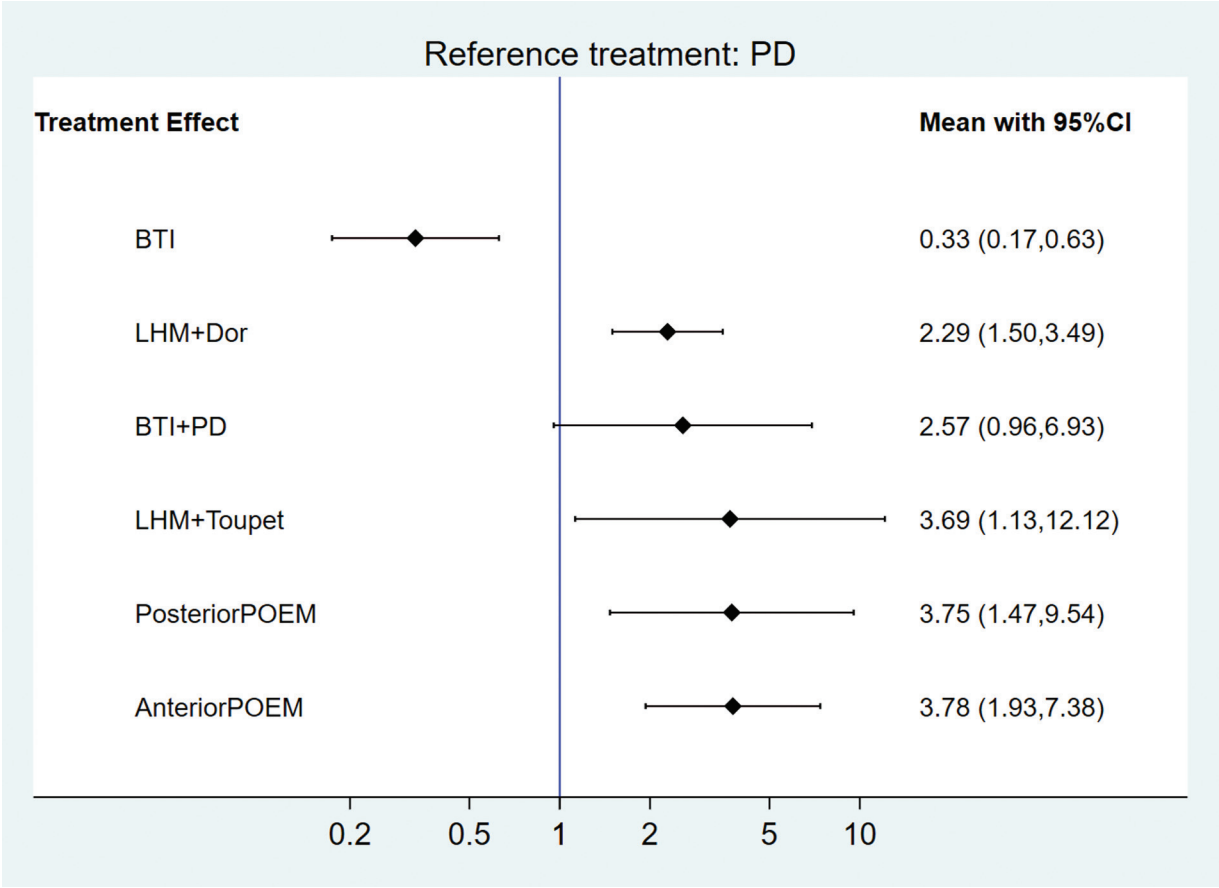


Figure 3. Network forest plot of indirect comparisons (ORs) of different therapeutic modalities for achalasia (≤1-year follow-up period). CI = confidence interval, ORs = odd ratios. The abbreviations of therapies are mentioned in Figure 2.

illustrated the design-by-treatment inconsistency model, loop inconsistency model, and side-splitting inconsistency). There was no significant inconsistency discovered when using the design-by-treatment inconsistency and loop-inconsistency models. Using the side-splitting method, we only found statistically significant inconsistency in the comparison of BTI versus BTI + sPD ($P < .05$) in subgroup analysis when PD was divided into either single or double sessions. In addition, the results of sensitivity analyses after excluding studies in abstract form (2 trials), articles including unavailable medical history (3 trials), Chagas' disease (2 trials), per-protocol analysis (2 trials), and trials with a <6-month follow-up period (3 trials), were also distributed similarly in their ranking to overall short-term efficacy.

3.3. Secondary outcome: safety

In this NMA, none of the interventions for achalasia, except LHM without fundoplication, were significantly associated with worsening of gastroesophageal acid reflux than PD (see Figure S2E, Supplemental Digital Content, http://links.lww.com/MD/G714). The medians (IQRs) for short-term gastroesophageal acid reflux events (%) of LHM, Anterior POEM, Posterior POEM, LHM + Toupet, LHM + Dor, and PD were 47.6, 30.0 (IQR, 29.5–31.7), 33.3 (IQR, 30.3–37.5), 9.5 (IQR, 5.8–24.0), 20.5 (IQR, 8.0–28.6), and 16.4 (IQR, 15.8–19.5), respectively. As for moderate-to-severe adverse events after treatment, we also observed that there was no statistical difference among the different therapeutic modalities for achalasia (see Figure S2F, Supplemental Digital Content, http://links.lww.com/MD/G715). Although the LHM + Toupet, LHM, and LHM + Dor groups appeared to increase the risk of side effects, no regimens were associated with significant increases. Our results also indicate that there were no significant inconsistencies when using the funnel plot (see Figures S4F–S4G, Supplemental Digital Content, http://links.lww.com/MD/G874, http://links.lww.com/MD/G875), Egger's test (see Figures S5F–S5G, Supplemental Digital Content, http://links.lww.com/MD/G735, http://links.lww.com/MD/G736), design-by-treatment inconsistency model, loop-inconsistency model, and side-splitting method in both secondary outcomes. The sensitivity analysis after excluding studies evaluating gastroesophageal acid reflux based on symptoms (2 trials) showed none of the interventions for achalasia were significantly associated with worsening of gastroesophageal acid reflux than PD.

4. Discussion

In this NMA, we comprehensively compared 8 treatments for achalasia dating back to the year 2000 in order to clarify the relative efficacy and safety in patients with idiopathic achalasia. We demonstrated that Anterior POEM, Posterior POEM, LHM

Table 1

League table of comparative efficacy of different therapeutic modalities for achalasia (≤1-year follow-up period)[*].

Posterior POEM	1.00 (0.54,1.84)					
0.99 (0.51,1.92)	**Anterior POEM**		1.33 (0.72,2.46)		**5.53 (2.17,14.12)** [b]	16.24 (0.81,325.88)
1.01 (0.24,4.37)	1.02 (0.28,3.78)	**LHM + Toupet**	0.84 (0.19,3.77)		**9.05 (1.55,52.80)** [b]	
1.64 (0.67,4.01)	1.65 (0.90,3.05)	1.62 (0.50,5.23)	**LHM + Dor**		**2.12 (1.19,3.78)** [b]	**4.67 (1.51,14.45)** [b]
1.46 (0.38,5.60)	1.47 (0.45,4.77)	1.44 (0.31,6.69)	0.89 (0.31,2.56)	**BTI + PD**	**3.26 (1.20,8.88)** [b]	**4.38 (1.32,14.50)** [b]
3.75 (1.47,9.54) [b]	**3.78 (1.93,7.38)** [b]	**3.69 (1.13,12.12)** [b]	**2.29 (1.50,3.49)** [b]	2.57 (0.96,6.93)	**PD**	**4.40 (1.68,11.52)** [b]
11.33 (3.75,34.27) [b]	**11.43 (4.66,28.05)** [b]	**11.18 (2.95,42.34)** [b]	**6.92 (3.41,14.03)** [b]	**7.78 (2.73,22.19)** [b]	**3.03 (1.59,5.74)** [b]	**BTI**

Results of the network meta-analyses are presented in the left lower half while reports of the pairwise meta-analyses are presented in the right upper half. Interventions (yellow cell) are ordered from the newest (left upper portion) to the oldest (right lower portion). Right hand side intervention was reference group. Blue cells indicate ORs significantly higher than 2.00.

BTI = botulinum toxin injection, LHM = laparoscopic Heller's myotomy, PD = pneumatic dilation, POEM = per-oral endoscopic myotomy.

[*] Outcomes are expressed as odds ratios (95% CIs).

[†] Statistically significant.

+ Toupet, and LHM + Dor were all significantly superior to PD in short-term efficacy, with Anterior POEM and LHM + Dor showing a higher improvement than PD in mid-term efficacy. BTI showed a significantly lower efficacy than PD in both follow-up periods. In addition, Anterior POEM and LHM + Toupet also achieved higher efficacy in comparison to PD in treatment-naïve individuals during short-term and mid-term efficacy. With respect to safety, none of the interventions for achalasia, except LHM without fundoplication, were significantly associated with a worsening of gastroesophageal acid reflux than PD. As for moderate-to-severe adverse events, there was an increasing trend in the LHM + Toupet, LHM without fundoplication, and LHM + Dor groups, although this was not statistically significant. Therefore, our NMA suggest that POEM using the anterior or posterior approach and LHM with Dor or Toupet fundoplication may be first recommended. Although PD or BTI + PD provided limited efficacy in symptom control, the treatments should still be considered in poor candidates for anesthesia. On the contrary, we recommended that BTI not be used as definitive therapy for patients with idiopathic achalasia.

According to American and European guidelines released in 2020,[30,31] POEM and LHM have comparative efficacy in terms of symptomatic improvement, but whether POEM or LHM should be recommended as a first priority remains inconclusive. Previous meta-analyses[13,32] have indicated that POEM proved more successful than LHM in dysphagia control, although the analyses mainly included retrospective studies with missed eligible RCTs, and variable follow-up periods. In addition, Park et al published that surgical time and length of hospitalization tended to be shorter for POEM patients in comparison to LHM patients without significance, except for the length of the myotomy procedure which was significantly longer in POEM patients. Mundre et al[14] concluded that there was no difference between POEM and LHM in efficacy, serious adverse events, GERD, and erosive esophagitis based upon 9 RCTs with moderate heterogeneity and a follow-up duration ranging from 1 to 3 years. In another consensus taken from Korea, POEM was superior to LHM only in the postoperative Eckardt score, with a longer length myotomy procedure and no differences in other aspects.[33] None of the above-mentioned studies took different modalities of procedures, or duration of follow-up into consideration. In our study, Anterior POEM, Posterior POEM, LHM + Toupet, and LHM + Dor were all significantly superior to PD in both short-term efficacy and mid-term efficacy, except for Posterior POEM and LHM + Toupet in mid-term efficacy, although none were significantly more effective than the others.

Two meta-analyses[34,35] regarding the clinical outcomes between Anterior POEM and Posterior POEM found that both were equally effective without any statistical significance in postsurgical GERD. Mohan et al wrote that the overall procedure time for Posterior POEM was shorter than that of Anterior POEM from RCTs and cohort studies, with Rodríguez de Santiago et al reinforcing that Posterior POEM has a shorter incision closure time and fever adverse events, although the length of hospitalization was slightly longer than Anterior POEM. Technically, the posterior approach maintains a better alignment of endoscopic accessories from mucosal incision to submucosal tunneling, as well as an easier orientation for mucosal closure. In order to reduce the incidence of postprocedural GERD, precisely locating the gastroesophageal junction in order to limit the length of myotomy at the gastric side[36] is important. Identification of the landmark of the two penetrating vessels during tunneling via the posterior approach[37] may be faster than use of a second endoscopy[38] so as to literally reassure the myotomy procedure time. All of the above procedures may be the reason as to why Posterior POEM exhibits a safer profile and quicker mucosal closure time, although other factors including selective myotomy of the inner circular muscle,[39] the length of myotomy at the esophageal side,[40] and manometric subtypes of achalasia[41] are also crucial, but not standardized, in present POEM procedure. However, we failed to demonstrate the priority of Posterior POEM in mid-term efficacy, treatment-naïve patients, and moderate-to-severe adverse events, which may be explained by the fact that there were no head-to-head comparisons with Posterior POEM other than Anterior POEM, as well as mid-term outcomes of Posterior POEM in treatment-naïve patients being longer than 1 year. Thus, further investigation is still warranted.

LHM with partial fundoplication has become the treatment of choice for idiopathic achalasia since the 1990s, and the evolution of LHM has shown that myotomy with fundoplication is superior to both myotomy without fundoplication and myotomy with Nissen fundoplication in order to separately avoid postsurgical acid reflux and dysphagia.[42] The choice between Dor and Toupet fundoplication after LHM remains inconclusive and depends upon the surgeon's expertise. Technically, the length of myotomy at the gastric side is usually longer than that of POEM, while the Dor approach usually requires a limited

hiatal dissection as well as complete coverage of the anterior exposed mucosa. In contrary, the Toupet approach is less standardized and time-consuming when looking to achieve circumferential esophageal mobilization, which may prevent scarring and adhesion of the separated muscle edge, while also reducing recurrent dysphagia.[42,43] Recently, two meta-analyses[44,45] have revealed equivalent results, while Siddaiah-Subramanya et al additionally reported that Toupet fundoplication is better than Dor in terms of length of hospitalization and quality of life. In our study, LHM + Toupet ranked higher than LHM + Dor in both short-term and mid-term efficacy, although not significantly, while only LHM without fundoplication showed worse gastroesophageal acid reflux than PD.

One Cochrane review in 2014[46] demonstrated that PD is more effective than BTI after 6 months of treating achalasia, which is consistent to our results during both the short-term and mid-term follow-up periods. Both could perform under endoscopic visualization and conscious sedation while the procedure times were similar between PD and BTI. However, there was no standard operating procedure for BTI from preparation to injection, and prolonged treatment sessions as well as relapsing symptoms might aggravate the risk of aspiration pneumonia and body weight loss in these patients. Currently, PD and LHM with partial fundoplication are both recommended in the Guidelines.[30,31,33] Although surgeons perform LHM step by step, it is still more difficult than PD, which requires experienced physicians and their collaborative team to accomplish the procedure. On the contrary, dilation techniques diverge greatly from balloon size, dilation durations, step-up regimens, single-session or double-sessions, to the interval between double-sessions, which complicates the outcomes of PD as well as inter-endoscopist experiences. One attempt at umbrella review[47] failed to achieve a reliable result between PD and LHM due to the variability in PD techniques and outcome definitions. In subgroup analysis of our study we used the treat-to-target approach to manage achalasia, involving essential components of PD techniques in order to achieve clinical success and further divide the PD regimen into single-session or double-session. Anterior POEM, Posterior POEM, LHM + Toupet, BTI + sPD, and LHM + Dor have better efficacy when compared to dPD, while there is no difference between sPD and dPD.

There are several limitations to this NMA. Firstly, we analyzed the achalasia treatments according to the different modalities of POEM, LHM, and PD, and did not include the robotic approach for LHM and short versus long esophageal myotomy[40] in our comparison. Short myotomy usually applies to type I and II achalasia, which we did not separate from the target population. In addition, only certain studies clarified the length of esophageal myotomy, which was an obstacle for merging short myotomy into our NMA. Secondly, we did not perform meta-regression according to achalasia subtypes or duration of symptoms, for the purpose of examining the impact of patient variables on study outcomes, due to missing characteristics. Instead, we performed subgroup analysis in treatment-naïve patients and sensitivity analyses after omitting articles involving patients who had an unavailable medical history or small portion of Chagas' disease in order to explore the impact of heterogeneity in a sample population. Thirdly, high risks were common in overall bias due to inadequate concealment, non-blindness of participants, and missing outcome data in most trials. Moreover, variability in outcome definitions and measurements assaulted the transitivity of NMA and rendered clinical outcomes unreliable, particularly in postsurgical acid reflux and adverse events. All of the above indicates that our results are based on a very low quality of evidence owing to a high risk of bias, indirectness, and impression amongst enrolled trials.[48] Nevertheless, we demonstrated an increasing trend towards the use of LHM, either with or without partial fundoplication, regarding moderate-to-severe adverse events and worse gastroesophageal acid reflux from LHM without fundoplication in comparison with PD. POEM using the anterior or posterior approach had slightly higher ORs of GERD than LHM with partial fundoplication.

5. Conclusions

In this NMA, we compared 8 different modalities of achalasia treatment, where the anterior and posterior approach for POEM, and LHM with Toupet and Dor fundoplication shown to be significantly superior to PD in short-term efficacy, with Anterior POEM and LHM + Dor showing better efficacy than PD in mid-term efficacy. As for safety issues, only LHM without fundoplication was significantly associated with higher gastroesophageal acid reflux than the PD and LHM + Toupet, LHM without fundoplication, and LHM + Dor groups, which showed a non-significant increase in moderate-to-severe adverse events. Our NMA may be of value to clinicians, as the findings suggest that POEM and LHM with partial fundoplication may be considered as a first line of treatment beyond the recommendations set by available guidelines.

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Author contributions

Performed critical revision of the manuscript and approved the final draft of the article: All authors.

Designed the meta-analysis: Chung-Wang Ko, Sz-Iuan Shiu, Chung-Hsin Chang, and Yu-Kang Tu.

Contributed to data acquisition and drafted the article: Sz-Iuan Shiu, Chung-Wang Ko, Chung-Hsin Chang, and Yu-Kang Tu.

Contributed to data analysis and interpretation: Sz-Iuan Shiu, Chung-Wang Ko, and Yu-Kang Tu

Conceptualization: Chung-Wang Ko, Sz-Iuan Shiu.

Data curation: Sz-Iuan Shiu, Chung-Hsin Chang.

Formal analysis: Sz-Iuan Shiu.

Investigation: Sz-Iuan Shiu, Chung-Hsin Chang, Yu-Kang Tu.

Methodology: Sz-Iuan Shiu, Yu-Kang Tu.

Project administration: Sz-Iuan Shiu.

Software: Sz-Iuan Shiu, Yu-Kang Tu.

Supervision: Chung-Wang Ko.

Validation: Chung-Wang Ko, Sz-Iuan Shiu, Chung-Hsin Chang, Yu-Kang Tu.

Writing – original draft: Sz-Iuan Shiu, Chung-Wang Ko.

Writing – review & editing: Chung-Wang Ko, Sz-Iuan Shiu.

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