Outcome of peroral endoscopic myotomy (POEM) in treatment-naïve patients. *A systematic review*

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Abstract

Objectives. Achalasia is a primary motility disorder of the esophagus characterized by aperistalsis and failure of lower esophageal sphincter (LES) relaxation. Treatment of achalasia aims at reducing LES pressure. The common treatment modalities are laparoscopic Heller myotomy and pneumatic dilatation, but during the last decade, a promising treatment, per oral endoscopic myotomy (POEM), has been introduced. The aim of the present study was to perform a systematic review of the literature to assess the outcome of POEM in treatment-naïve patients.

Materials and Methods. A systematic literature search in PubMed, Embase and Cochrane databases was performed using the terms ‘Achalasia AND (POEM OR peroral endoscopic myotomy OR per-oral endoscopic myotomy)’. Inclusion criteria were: original article; English language; $n \geq 20$ with $\geq 90\%$ treatment-naïve patients; follow-up ≥ 3 months; and outcome evaluation of POEM including symptom score and objective tests. Exclusion criteria were: reviews and metaanalyses; pediatric data; duplicates; and articles with overlapping data material.

Results. Of the 1641 articles identified, seven were included. The included studies all reported a short term clinical success of $> 90\%$. Clinical success including post POEM reflux was mainly estimated by symptom scorings. There were few procedure-related complications.

Conclusions. The studies of treatment-naïve patients indicate a high rate of clinical success. Nevertheless, a more systematic and standardized evaluation is recommended to improve the reports on outcome of POEM. The follow-up rate should be high and the evaluation protocol should include both symptom scoring and objective testing with predefined treatment goals.

Keywords

Achalasia, Peroral endoscopic myotomy, POEM, High resolution manometry, Timed barium esophagogram, 24-h pH monitoring, Treatment-naïve, Esophageal physiology.

Introduction

Achalasia is a primary motility disorder of the esophagus with an incidence of 0.5 – 1.6/100 000 and a prevalence of 9 – 11/100 000 (1, 2). The autoimmune destruction of myenteric neurons is the crucial part of the pathogenesis, and it seems to be triggered in genetically susceptible individuals by an extrinsic factor such as a viral infection (3-6). Aperistalsis and failure of lower esophageal sphincter (LES) relaxation cause the symptoms of achalasia, which are included in the Eckardt score (ES): dysphagia, regurgitation, chest pain and weight loss.

Treatment of achalasia aims at reducing LES pressure. Medical treatment is mainly ineffective and injection of botulinum toxin into LES should preferably be reserved older and multimorbid patients due to its temporary effect, leaving laparoscopic Heller myotomy (LHM), pneumatic dilatation (PD) and per oral endoscopic myotomy (POEM) as the most relevant treatment modalities (7-10). LHM and PD have comparable outcome when PD is performed as a graded dilatation procedure and dilatation is repeated in case of recurrent symptoms (11-13). A partial fundoplication is commonly added to LHM to prevent postoperative reflux. Clinical successful outcome of LHM exceeds 90 % in the short-term and decreases to about 80 % after 5 years and beyond (14-17). The long-term efficacy rate of a single pneumatic dilatation is inferior, especially in patients younger than 40 years. Consequently, LHM is by many considered the gold standard in achalasia treatment and the modality to which POEM should be compared (18, 19).

POEM was clinically introduced in 2008 as a new achalasia treatment modality (20). The method is now established internationally, and more than 6000 procedures have been performed worldwide (21). There are yet no published randomized, controlled trials comparing the outcome of POEM with LHM or PD. Follow-up studies have, however,

confirmed the equivalent clinical outcome of POEM to LHM in the short-term (22-26).

Furthermore, POEM has been demonstrated to be at least as effective as PD (27), and long-term POEM outcome data are now emerging (28, 29).

Numerous studies have demonstrated that both endoscopic achalasia therapy and surgical myotomy imply significant reduced success rate of a following LHM (30-34). Accordingly, the outcome of POEM may also be influenced by previous procedures, a supposition supported by a recent study of a large POEM cohort, indicating that previous achalasia treatment is a negative outcome predictor (35). With the objective to evaluate the efficacy of POEM itself, an exploration of the available reports on POEM in treatment-naïve achalasia patients is warranted. Thus, the aim of the present study was to perform a systematic review of the literature to assess the outcome of POEM in treatment-naïve patients.

Materials and methods

The systematic review was carried out in accordance with the guidelines of the preferred reported items for systematic review and meta-analyses (PRISMA-P) (36).

A systematic literature search in PubMed, Embase and Cochrane databases was performed using the terms ‘Achalasia AND (POEM OR peroral endoscopic myotomy OR per-oral endoscopic myotomy)’ (18.11.17). The title and abstract of identified articles were first reviewed. If the articles were still eligible after this screening, the full-text articles were reviewed. A reject log of all excluded articles was prepared and is available by contacting the corresponding author.

The following inclusion criteria were applied: original article; English language; $n \geq 20$ with $\geq 90\%$ treatment-naïve patients or studies with higher number included with separate data presentation on treatment-naïve patients; follow-up ≥ 3 months; and outcome evaluation of POEM including symptom score (e.g. ES and objective tests (high resolution manometry (HRM) or timed barium esophagogram (TBE))).

The following exclusion criteria were applied: reviews and metaanalyses; pediatric data (age < 18 years); duplicates; and articles with overlapping data material (exclusion of the article with the lowest number of patients included).

The reference lists of all included articles were scrutinized for articles not found in the electronic search.

The following evaluation variables were included in the review: percentage of patients with $ES \leq 3$; ES before and after POEM; follow-up period; timing of clinical evaluation; percentage of patients with clinical evaluation; timing of objective tests; percentage of patients with objective tests (TBE or HRM); LES pressure (resting pressure and integrated relaxation pressure/residual pressure) before and after POEM; TBE before and after POEM

(reduction in barium column height); procedure-related complications; reflux symptoms after POEM; reflux esophagitis after POEM and positive 24 h pH monitoring after POEM.

Results

When applying the search criteria, 1641 articles were identified (Figure 1). After screening titles and abstracts, 74 articles were still assessed eligible. When performing the full-text screening, another 67 articles were excluded. Hence, seven articles were included in the evaluation (27, 37-42).

The number of patients studied in the included articles ranged from 30 to 87 patients and the sum of all treatment-naïve achalasia patients was 355 (Table 1). All studies had a retrospective design except for the prospective study by Ling et al (37). The studies by Shiwaku et al and Liu et al were the only studies to include information concerning disease stage. They reported inclusion of five and two patients with a sigmoid esophagus, respectively (38, 39).

The identified studies all presented a short-term clinical success rate of $> 90\%$ (Table 2). Clinical success was defined as an Eckardt score ≤ 3 . Zhang et al demonstrated a 91 % clinical efficacy in subtype 3 achalasia with a mean myotomy length of 8.2 cm (40). All patients in the included studies were available for symptom assessment prior to POEM and during follow-up, except for two patients in the series of Teitelbaum et al (41). HRM was applied pre and post POEM in the included studies, describing a significant decrease in LES-pressure after POEM. In the four studies presenting percentage of patients evaluated by objective tests post POEM, this number varied between 47 and 100 % (27, 40-42).

Additionally, Ling et al and Meng et al reported the post-POEM LES-pressure categorically, demonstrating a LES-pressure < 10 mm Hg in 99 and 88 % of the patients, respectively (27, 37). Only two studies included a TBE protocol with barium height analysis in their outcome evaluation (37, 41). The included studies reported standard timing of physiologic testing post POEM, except for Shiwaku et al and Ling et al (37, 38). The follow-up period varied between three and 51 months. The only study with a minimum of 24 months follow-up was on

achalasia subtype 3 exclusively (40).

Six of the included studies presented procedure-related complications and reflux symptoms after POEM in the treatment-naive patients (Table 3). Clavien Dindo (CD) classification grade 1 occurred in 5 % of the patients. Overall, CD grade 3b was the most serious complication reported. The frequency of post POEM reflux symptoms varied from 3 to 19 %. In two studies, a validated reflux questionnaire (gastroesophageal reflux disease questionnaire (GerdQ)) was applied to record symptoms (27, 41). In two studies, post POEM reflux was also evaluated endoscopically (40, 41). Esophagitis beyond grade A according to the Los Angeles classification was demonstrated in 9 % of the patients. Furthermore, one study also included the common variables of 24-h pH monitoring (41).

Discussion

The present review demonstrates that there are only a limited number of studies available reporting the outcome of POEM in treatment-naïve achalasia patients. Except for one, these studies are all retrospective. Furthermore, the follow-up rate for symptom score is high, whereas it is low or not given for objective evaluations, which makes it difficult to conclude on treatment efficacy. The occurrence of procedure-related complications is low, and the frequency of reflux symptoms and esophagitis seems to be modest. In general, the available results indicate a positive outcome after POEM, which is in line with the results reported in the large body of POEM publications including patients with and without previous treatment (43-47).

In the included articles in the present review, a low frequency of procedure-related complications and serious post POEM reflux was reported. However, the majority of the studies evaluated post POEM reflux only by symptom registration and without applying a validated questionnaire. Information on the overall frequency of use of proton pump inhibitors and antacids would also have been interesting. In the studies including data on upper endoscopy, patients with positive findings usually had a mild degree of reflux esophagitis (Los Angeles classification grade A) with effective symptomatic relief of proton pump inhibitors. In general, availability of reflux data are unfortunately limited and do not allow firm conclusions to be drawn about frequency and severity of post POEM reflux, which has been a major concern in other reports (48, 49).

The limited application of objective tests in the outcome evaluation of POEM is evident in well-known patient-cohorts (47, 50) and studies reporting equal efficacy of POEM in both treatment-naïve patients and patients with multiple previous therapies, including LHM (51-59). In their impressive series of 500 patients, Inoue et al reported a long-term clinical POEM success of 89 % based on the 105 patients with equal to or more than three years of follow-up,

of whom 58 % and 15 % were available for clinical evaluation and HRM, respectively (47). It is noteworthy that many of the large scale POEM studies do not present separate data on treatment-naïve patients and despite the high number of patients involved, these studies could not be included in the present review.

In correspondence with the present review, the almost uniformly reported clinical efficacy rate of about 90 % in POEM cohorts is based mainly on the ES (60), which includes symptoms and signs largely reported by the patient and recorded by the physician or an assistant. The ES is an important clinical variable, reliably used in a large number of achalasia studies. It has, however, been demonstrated that physicians tend to report a more marked symptom improvement than patients (61). Accordingly, also the recording of the ES may potentially be influenced by the physicians' expectations of a positive treatment effect. Furthermore, the commonly applied definition of clinical success of ES as three or less is well known among dedicated physicians, which may bias the recordings by the physician.

It may be speculated why the reviewed studies only included objective tests to a limited degree. A possible explanation is that implementation of e.g. TBE and HRM post POEM is challenging. POEM is performed mainly in highly specialized centers, and follow-up requiring that the patients are revisiting the center a period after treatment, is difficult as it may include long travels and extra costs. Furthermore, the procedures may be regarded as unpleasant.

As previously discussed, the ES (60) is the symptom score most widely used when evaluating outcome of achalasia treatment. Nevertheless, the TBE may also be used as a valuable tool for evaluation, and Vaezi et al have reported that TBE may outperform symptom assessment in the prediction of long term achalasia treatment success (62). Furthermore, Andersson et al reported that less than 50 % improvement in barium height at one minute evaluation reflects a 40 % risk of failure in patients treated with PD (63). It should, however, be noted that the

studies by Vaezi et al and Andersson et al did not use the ES for symptom evaluation. Post-treatment LES pressure is also an important predictor for both short- and long-term efficacy (19, 46), though the expected post-treatment LES-pressure profiles may differ depending on treatment modality (25). Interestingly, it is not established whether the residual pressure or the resting pressure of LES is superior for effect evaluation. Furthermore, analysis of the cross sectional area of the esophagogastric junction and its distensibility is now gradually introduced and may predict POEM outcome more accurately and help tailor the myotomy (64, 65).

Conclusion

The present systematic review demonstrates that there are few available studies reporting the effect of POEM in treatment-naïve patients. Most studies are retrospective, have a low follow-up rate for objective tests and are thus mainly based on symptom scorings, which may be biased by the recording physician. Hence, a definite conclusion of the effect of POEM in treatment-naïve patients can at present hardly be drawn. Nevertheless, the limited data available suggest similar outcome compared with studies including both treated and treatment-naïve patients.

Recommendations

To improve the evaluation of outcome of POEM, a more systematic and standardized evaluation is recommended, and the follow-up rate should be higher than 80% in future studies (66). Furthermore, we suggest that the evaluation protocol should include both symptom scoring and objective testing (HRM and TBE), and treatment goals should be elaborated also for these objective tests. A post treatment resting pressure of LES lower than 10 mm Hg has been proposed and seems reasonable also according to our clinical experience

(19). For TBE, a 50% reduction in the one minute barium column height is suggested (63).

Furthermore, evaluation of reflux should also be added (upper endoscopy and 24-h pH monitoring) as post POEM reflux is a major concern and frequent use of proton pump inhibitors is necessary (67). Moreover, a minimum duration of the follow-up period is required also when reporting short term results. To ensure that the esophagus has recovered after the procedure performed, we suggest that objective testing is performed after at least three months. In addition to the established composite ES, a patient reported symptom scoring should also be included.

Disclosure of interest

The authors report no conflict of interest.

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Table 1. Characteristics of included studies

First author, year, country	Study design	Total number of patients (n)	Treatment naive (n)	Female (n)	Age (years)	Symptom duration (years)	Subtype (n)	Length of myotomy (cm)
Meng, 2017 China (27)	Retrospective	72	32	19	44.8 ± 11.6	2 (1-5) ¹	T1 : 5 T2 : 18 T3 : 9	8 ²
Ling, 2014 China (37)	Prospective	87	87	47	41.6 ± 15.6	na	na	na
Shiwaku, 2016 Japan (38)	Retrospective	100	72	47	48 ± 19	7.6 ± 9.1	T1: 5 T2: 57 T3: 10	12.9 ± 3.7
Liu, 2015 China (39)	Retrospective	35	33	24	40.2 (15 - 63) ³	8.5 (0.2-20) ³	na	na
Zhang, 2017 China (40)	Retrospective	32	31	16	43.3 (16-79) ³	2.0 (0.2 -28.0) ⁴	T3 : 32	8.2 (3-15) ³
Teitelbaum, 2014 USA (41)	Retrospective	41	37	12	45 ± 15	3 ± 6	T1 : 10 T2 : 25 T3 : 1	9 ⁵
Tang, 2015 China (42)	Retrospective	67	63	31	40.3 ± 10.9 ⁶	0.7 ± 0.5 ⁶	T1 : 36 T2 : 31 T3 : 0	9.4 ± 2.2 ⁶

Continuous variables presented as mean ± SD if not stated otherwise. ¹Interquartile range. ²Median. ³Mean (range). ⁴Median (range). ⁵Standardized length. ⁶Data for first series given.
na: not available

Table 2. Clinical and objective test variables

First author, year, country	Eckardt score ≤ 3 post POEM (%)	Eckardt score pre <i>and</i> post POEM	Follow-up (months)	Clin. evaluation post POEM (months)	Clinical follow-up rate (%)	Objective tests post POEM (months)	Objective tests follow-up rate (%)	Resting LES pressure pre <i>and</i> post POEM (mean mm Hg)	TBE ⁵ one min pre <i>and</i> post poem (cm)
Meng, 2017 China (27)	96-93	6.9 $\pm$ 2.1 1.1 $\pm$ 1.0	25 $\pm$ 11	3+6+12+24+36	100	3+6	100	28.0 $\pm$ 10.9 12.6 $\pm$ 6.5	na
Ling, 2014 China (37)	95	7.1 $\pm$ 2.1 0.8 $\pm$ 0.9	14 $\pm$ 4	12-19	100	12-19	na	32.4 $\pm$ 15.3 3.8 $\pm$ 3.9	11.7 $\pm$ 1.2 3.8 $\pm$ 1.3
Shiwaku, 2016 Japan (38)	96	5.9 $\pm$ 2.5 0.8 $\pm$ 0.9	3	3	na	na	na	24.2 $\pm$ 13.3 ¹ 10.8 $\pm$ 6.1 ¹	na
Liu, 2015 China (39)	100	6.8 $\pm$ 1.8 0.5 $\pm$ 0.6	11.4 (6-15) ²	1+6	100	1+6	na	29.5 $\pm$ 12.6 10.3 $\pm$ 11.7	na
Zhang, 2017 China (40)	91	7.2 (4-11) ¹ 1.4 (0-5) ¹	27 (24-51) ³	24-51	100	3	47	39.2 (19.4-78.0) ² 19.0 (10.8-30.6) ²	na
Teitelbaum, 2014 USA (41)	92	7 $\pm$ 2 1 $\pm$ 2	15 (12-33) ²	12-33	95	12	51	22 $\pm$ 10 9 $\pm$ 6	20 $\pm$ 6 6 $\pm$ 4
Tang, 2015 China (42)	94	7.3 $\pm$ 2.2 ⁴ 1.3 $\pm$ 1.1	12	6+12	100	6+12	70	37.3 $\pm$ 16.4 ⁴ 15.2 $\pm$ 7.7	na

Continuous variables presented as mean $\pm$ SD if not stated otherwise. ¹Lower esophageal sphincter *residual* pressure. ²Mean (range). ³Median (range). ⁴Data for first series given. ⁵Timed barium esophagogram. na: not available.

Table 3. Procedure-related complications and postoperative reflux

First author, year, country	Procedure related complications <i>Clavien-Dindo classification (CD)</i> (n (%))	Reflux symptoms (n (%))	Reflux esophagitis <i>Los Angeles classification (LA)</i> (n (%))	Positive 24-h pH monitoring (n (%))
Meng, 2017, China (27)	0	6 (19)	na	na
Ling, 2014, China (37)	CD 1: 1 (1) CD 3a: 2 (2)	9 (10)	na	na
Shiwaku, 2016, Japan (38)*	-	-	-	-
Liu, 2015, China (39)	CD 1: 1 (3)	1 (3)	na	na
Zhang, 2017, China (40)	CD 1: 4 (13) CD 3a: 2 (6)	6 (19)	LA A: 2 (6) LA B: 3 (9)	na
Teitelbaum, 2014, USA (41)	CD 1: 7 (17) CD 3b: 1 (2)	6 (15)	LA A: 11 (50) LA D: 2 (9)	4 (31)
Tang, 2015, China (42)	CD 1: 2 (3)	4 (6)	na	na

*Treatment-naive not presented separately. na: not available.

Figure 1. Flow chart of systematic review