Role of Peroral Endoscopic Myotomy in Geriatric Patients with Achalasia: A Systematic Review and Meta-Analysis

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Keywords

Achalasia · Peroral endoscopic myotomy · Geriatric patients · Systematic review · Meta-analysis

Abstract

Background: Peroral endoscopic myotomy (POEM) is a particularly attractive intervention for achalasia. Presently, POEM has been reported to be effective and safe for achalasia in geriatric patients. Herein, this systematic review was conducted to explore the role of POEM in geriatric patients with achalasia. **Method:** PubMed, Embase, and Cochrane Library were searched to identify studies evaluating the clinical outcome of POEM in geriatric patients with achalasia during January 2009 to October 2020. The primary outcomes were technical and clinical success. Secondary outcomes included postoperative Eckardt score, lower esophageal sphincter (LES) pressure, adverse events, and clinical reflux. **Results:** There were 7 studies with a total of 469 geriatric patients, and the pooled technical success of POEM treatment was 98.1% (95% confidence interval [CI], 95.1–99.3%), and the pooled clinical success was 92.5% (95% CI, 89.3–94.8%). After POEM, the Eckardt score significantly decreased by 6.09 points (95% CI, 5.44–6.74, $p < 0.00001$), and the LES pressure significantly reduced by 13.53 mm Hg (95% CI, 5.14–

21.91, $p = 0.002$). The pooled adverse events rate was 9.0% (95% CI, 4.3–17.9%), and the post-POEM clinical reflux rate was 17.4% (95% CI, 12.9–23.2%). **Conclusion:** Our current study demonstrated that POEM was an effective and safe technique for achalasia in geriatric patients.

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Introduction

Achalasia is an esophageal motility disorder, characterized by insufficient relaxation of the lower esophageal sphincter (LES), resulting in obstructed bolus transport and stasis of food in the esophagus [1, 2]. It occurs very rarely, with an estimated incidence rate of 0.77–1.35 per 100,000 population and a prevalence of 1.41–4.60 per 100,000 population. Achalasia can occur in all patient age-groups, with highest incidence in the seventh decade of life [3–5]. The most common clinical symptoms for achalasia include dysphagia, regurgitation, aspiration pneumonia, chest pain, and weight loss [6]. The course of this disease is generally chronic, progressive dysphagia

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and weight loss over several months to years, which significantly impairs life quality. Therefore, proper treatment is of vital importance for achalasia.

Current therapeutic options include medical treatment, botulinum toxin injection, pneumatic dilation, peroral endoscopic myotomy (POEM), and laparoscopic Heller myotomy (LHM). LHM can achieve a relatively lasting effect but limited by the risk of perforation (4–7%) or surgical morbidity in geriatric patients [7–9]. Recently, a novel less invasive technique, POEM has been widely accepted for treating achalasia with an excellent safety profile, durability, and efficacy in adults [10–12]. Whether the same success can be achieved in geriatric patients requires further exploration. At present, some articles have explored the safety and efficacy of POEM in geriatric patients [13–19]. Therefore, we conducted this meta-analysis to summarize the safety and effectiveness of POEM in geriatric patients with achalasia.

Methods

Search Strategy

We conducted a systematic literature search in PubMed, Embase, and Cochrane Library covering the period from January 2009 to October 2020. The key words included “achalasia,” “POEM,” “per-oral endoscopic myotomy,” and “peroral endoscopic myotomy.” These words were used in all possible combinations to obtain the maximal number of studies (see online suppl. Table 1; see www.karger.com/doi/10.1159/000516024 for all online suppl. material). The word “geriatric” was not involved in our search to ensure a thorough search of the research available for POEM. This systematic review was carried out according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [20]. Our research does not require IRB approval and written consent.

Study Selection

The title and abstract of identified studies were first reviewed. If the studies were still eligible after screening, the full-text articles were reviewed in accordance with our inclusion and exclusion criteria. The inclusion criteria were as follows: (1) population: geriatric patients diagnosed with achalasia and aged ≥ 65 years; (2) intervention: POEM; and (3) outcome: technical and clinical success, Eckardt score, LES pressure, adverse events, and clinical reflux. Animal studies, case reports with < 5 patients, reviews and meta-analyses, duplicates, and studies that did not provide the available data for meta-analysis were excluded. Two reviewers independently conducted the article screening and data extraction. Any differences between reviewers were resolved by discussing with a third reviewer.

Data Extraction and Definition

The following data were extracted from the included articles: characteristics of the study (first author, year of publication, country, study duration, study design, number of patients, age, and gen-

der), preoperative and operative data (duration of symptoms, number of treatment-naïve patients, achalasia type, American Society of Anesthesiology Physical Status Classification System [ASA] scores, sigmoid-shaped esophagus, length of myotomy, operative time, length of hospital stay, and type of myotomy), and clinical outcomes (technical success rate, clinical success rate, pre- and postoperative Eckardt scores, pre- and postoperative LES pressure, adverse events, post-POEM clinical reflux, and follow-up time). The type of myotomy included full-thickness myotomy or selective circular bundles myotomy. Technical success was defined as completion of the whole POEM procedure. Clinical success was defined as an Eckardt score ≤ 3 during follow-up after the POEM procedure. The severity of adverse events was graded according to the American Society for Gastrointestinal Endoscopy (ASGE) lexicon [21]. Clinical reflux included symptomatic reflux and reflux esophagitis.

Assessment of Study Quality

Quality assessment was done by 2 reviewers independently using the National Institutes of Health (NIH) quality assessment tool, which was suitable for before-after studies with no control group [22]. Quality assessment of studies is highlighted in online suppl. Table 2.

Statistical Analysis

The statistical analysis was conducted using Review Manager 5.3 and Comprehensive Meta-Analysis software version 2, with a significance degree set at $p < 0.05$. The random-effects model was applied to this meta-analysis because the random-effects model provides more conservative estimations and was considered to be more realistic in this scenario [23]. For meta-analyses of dichotomous variables, such as technical success rate, clinical success rate, adverse events, and clinical reflux rate, the pooled event rates with a 95% confidence interval (CI) were calculated. For meta-analyses of continuous variables, including Eckardt scores and LES pressure, the mean difference with 95% CI was calculated. If study data are expressed as a median and range, they were converted to standard deviation before analysis. Heterogeneity was assessed using I^2 statistics. The I^2 score values of 0–30, 30–50, 50–75, and 75–100% were reflective of low, moderate, substantial, and high heterogeneity, respectively, according to the *Cochrane Handbook for Systematic Reviews of Interventions* [24]. Funnel plots was used to evaluate publication bias.

Results

Characteristics of Included Studies

Figure 1 shows the PRISMA flow diagram of our literature search. In summary, the initial search revealed 3,220 studies, of which 2,712 were screened for eligibility criteria after removing duplicates. After screening the titles and abstracts, 2,698 studies were excluded according to the predefined criteria and 14 full-text studies fulfilled criteria for eligibility assessment. Finally, 7 studies that fulfilled eligibility criteria were included for qualitative analysis (meta-analysis) [13–19].

Fig. 1. PRISMA statement of the study. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1 shows the baseline characteristics of the included studies. Among them, 3 studies were performed in the United States, 2 in China, 1 in Italy, and 1 in Japan. And these studies were published between 2016 and 2020. The included studies recruited patients from 2010 to 2019. All included studies were retrospective cohort studies, with 2 of the articles published as conference abstracts. All studies explored the efficacy and safety of POEM on geriatric patients.

Patients Baseline Characteristics

Of the 469 geriatric patients included in our studies, 235 (50.1%) patients were male. The mean age ranged from 67.9 to 84 years, and the duration of symptoms ranged from 5.5 to 30 months. Treatment-naiveness was reported in 5 articles, and there were 58.0% (185/319) of patients without receiving previous interventions before POEM. Achalasia types were reported in 2 studies, among which 18 patients were type I, 43 were type II, and 13 were type III. A sigmoid-shaped esophagus was reported in 4 studies, and there were 18.6% (45/242) of patients with a sigmoid-shaped esophagus (Table 1, 2).

Operative Data

Table 2 shows the detailed operative data of the POEM procedure. The mean myotomy length was reported in 6 studies, which ranged from 10 to 14.5 cm. The mean operative time was reported in 4 studies, which ranged from 50 to 103.7 min. And the hospital stay was reported in 5 studies, which ranged from 1 to 9.8 days. The type of myotomy was reported in 3 studies, in which full-thickness myotomy was applied in 137 geriatric patients and circular myotomy in 99 geriatric patients.

Clinical Outcome

Table 3 shows the clinical outcomes of POEM for achalasia in geriatric patients. Of all included studies, 5 studies reported postoperative Eckardt scores and 4 studies reported postoperative LES pressure. The pooled technical success of POEM treatment for achalasia was 98.1% (95% confidence interval [CI], 95.1–99.3%, $I^2 = 29.795\%$) (Fig. 2a), and the pooled clinical success was 92.5% (95% CI, 89.3–94.8%, $I^2 = 0\%$) (Fig. 2b).

The follow-up time was reported in 5 studies, which ranged from 2.4 to 41 months. In order to compare the differences of the clinical outcomes in different follow-up

Table 1. Baseline characteristics of included studies

Study	Year of publication	Country	Duration	Study design	Patient, <i>n</i>	Age, years	Gender (M:F)
Wang et al. [13]	2016	China	Jan 2010–Dec 2015	Retrospective	21	67.9±4.3	12:9
Chen et al. [14]	2018	The USA	Jan 2010–Jan 2016	Retrospective	76	84±3.2	40:36
Landi et al. [15]	2018	Italy	May 2011–Apr 2017	Retrospective*	88	72.2±4.7	39:49
Liu et al. [16]	2019	China	Aug 2010–Dec 2017	Retrospective	139	70.22±5.68	65:74
Klair et al. [17]	2019	The USA	Dec 2014–Oct 2018	Retrospective*	62	72.3±5.7	36:26
Abe et al. [18]	2020	Japan	Apr 2015–Mar 2019	Retrospective	28	≥80	12:16
Sanaka et al. [19]	2020	The USA	Apr 2014–May 2019	Retrospective	55	74 [#] (IQR 70–79)	31:24

M:F, male to female; IQR, interquartile range. * Published conference abstracts. [#] Median.

periods, we performed a subgroup analysis, in which the follow-up time was divided into less than 1 year, 1–3 years, and greater than 3 years (online suppl. Table 2). The pooled clinical success rate of POEM for geriatric patients with achalasia at different follow-up points was 95.4% (95% CI, 91.9–97.4%, $I^2 = 0\%$), 92.3% (95% CI, 86.9–95.6%, $I^2 = 0\%$), and 92.8% (95% CI, 85.2–96.6%, $I^2 = 0\%$), respectively (online suppl. Fig. 1). After POEM, the Eckardt score in geriatric patients was significantly decreased by 6.09 points (95% CI, 5.44–6.74, $p < 0.00001$, $I^2 = 83\%$) (Fig. 3a), and the LES pressure was significantly reduced by 13.53 mm Hg (95% CI, 5.14–21.91, $p = 0.002$, $I^2 = 97\%$) (Fig. 3b).

Adverse Events and Clinical Reflux

According to ASGE lexicon, the adverse events were classified as mild, moderate, severe, and fatal. As shown in online suppl. Table 3, a total of 45 adverse events were reported in geriatric patients. Most of the adverse events were mild (35.5%, 16/45) or moderate (60.0%, 27/45), and only 2 events were graded as severe (4.4%, 2/58). There was no fatal event. Overall, as shown in Figure 2c, the pooled adverse event rate related to POEM was 9.0% (95% CI, 4.3–17.9%, $I^2 = 74.612\%$). There were 4 studies that reported the clinical reflux. After POEM, a total of 44/256 geriatric patients experienced clinical reflux, and the pool rate was 17.4% (95% CI, 12.9–23.2%, $I^2 = 10.128\%$) (Fig. 2d).

Quality of Included Studies and Publication Bias

Online suppl. Table 4 shows the quality assessment of each study according to the NIH quality assessment tool. Of 7 involved studies, only one study [14] was of good quality and the remaining 6 studies [13, 15–19] were of

fair quality. There was symmetry in our funnel plots, which suggested that publication bias could be generally not considered (online suppl. Fig. 2).

Discussion

It has been reported that there is a peak in the incidence of achalasia among the geriatric population. Therefore, it is of vital importance to treat achalasia in geriatric patients [3–5]. The aim of therapy for achalasia is to reduce the LES pressure, with relieving symptoms, improving esophageal emptying, and preventing the development of mega-esophagus [25]. Medical treatment has been largely abandoned because of its poor efficacy and significant side effects [26]. LHM is the most successful treatment for geriatric patients without surgical contraindications [27]. However, LHM is an invasive procedure, accompanied by operative complications, not even suitable for these geriatric patients with high risk of anesthesia and operation. Therefore, endoscopic treatment is recommended as the first-line choice for geriatric patients with comorbidities [28]. Botulinum toxin injection and endoscopic pneumatic dilation are effective and safe in geriatric patients, but the effect is not long-lasting and often need repeated treatment [29, 30]. POEM has been a promising novel endoscopic treatment for achalasia with excellent outcomes [31, 32]. But it is unclear whether POEM is an appropriate and safe treatment modality for geriatric patients. Currently, our systematic review and meta-analysis revealed that (a) the pooled technical success of POEM for geriatric patients was 98.1% and the pooled clinical success was 92.5% (long-term efficacy was 92.8% at 3-year follow-up), and (b) the pooled adverse

Table 2. Pre-operative and operative data in included studies

Study	Duration of symptoms, months	Treatment-naïve patients, <i>n</i>	Achalasia type, I/II/III	ASA scores, I/II/III	Sigmoid-shaped esophagus	Myotomy length, cm	Operative time, min	Hospital stay, days	Type of myotomy (FTMG:CMG)
Wang et al. [13]	13.9±11.7	13	5/16/0	-	19.0% (4/21)	-	-	-	9:12
Chen et al. [14]	24.0 (IQR 17.8–30.3)	34	13/27/13	3/34/39	31.5% (17/54)	Esophageal: 10.0±4.0 Gastric: 2.7±0.8	103.7±47.9	3	13:63
Landi et al. [15]	-	-	-	-	-	12.3±3	-	-	-
Liu et al. [16]	8* (IQR 2–20)	105	-	-	11.51% (16/139)	10.57±1.81	50* (IQR 36–76)	3* (IQR 2–4)	115:24
Klair et al. [17]	-	-	-	-	-	13.8	-	1.9	-
Abe et al. [18]	5.5* (range 0.25–59)	16	-	-	28.6% (8/28)	14.5* (range 4–26)	60.5* (range 36–124)	9.8 (range 4–51)	-
Sanaka et al. [19]	30* (IQR 12–60)	17	-	13/24/11	-	10* (IQR 8–10)	90* (IQR 67.5–110)	1* (IQR 1–2)	-

ASA, American Society of Anesthesiology Physical Status Classification System; FTMG, full-thickness myotomy group; CMG, circular myotomy group; IQR, interquartile range. * Median.

Table 3. Clinical outcomes of included studies

Study	Technical success	Clinical success	Preoperative Eckardt score	Postoperative Eckardt score	Preoperative LES pressure, mm Hg	Postoperative LES pressure, mm Hg	Adverse events	Clinical reflux	Follow-up, months
Wang et al. [13]	100% (21/21)	95.2% (20/21)	7.7±1.7	0.77±0.83	29.9±3.7	10.3±1.6	4.8% (1/21)	9.5% (2/21)	21.8
Chen et al. [14]	93.4% (71/76)	90.8% (59/65)	7.0±2.3	0.8±1.0 (<i>n</i> = 65)	24.2±15.0	11.6±8.9 (<i>n</i> = 21)	14.5% (11/76)	16.1% (13/76)	8.5 (IQR 2.2–18.2)
Landi et al. [15]	100% (88/88)	95.4% (84/88)	8±2.0	-	-	-	-	-	24
Liu et al. [16]	99.3% (138/139)	92.9% (79/85)	7.16±1.94	0.56±1.27 (<i>n</i> = 85)	15.7* (IQR 9.9–27.65)	9.05* (IQR 8.05–11.45)	2.88% (4/139)	23.53% (20/85)	41* (IQR 26–60)
Klair et al. [17]	100% (62/62)	88.7% (55/62)	6.98±2.2	1.25±2	-	-	8.1% (5/62)	-	-
Abe et al. [18]	100% (28/28)	100% (17/17)	5* (range 3–9)	0* (range 0–2) (<i>n</i> = 17)	-	-	28.6% (8/28)	13.0% (3/23)	-
Sanaka et al. [19]	100% (55/55)	94.7% (36/38)	6* (IQR 4–8) (<i>n</i> = 54)	-	22.5* (IQR 15.7–30.5) (<i>n</i> = 49)	-	5.5% (3/55)	11.8% (6/51)	2.4* (IQR 2.2–2.7)

LES, lower esophageal sphincter; IQR interquartile range. * Median.

Fig. 2. a Forest plot of technical success of POEM for achalasia in geriatric patients. **b** Forest plot of overall clinical success of POEM for achalasia in geriatric patients. **c** Forest plot of the adverse events rate related to POEM in geriatric patients with achalasia. **d** Forest plot of the clinical reflux rate related to POEM in geriatric patients with achalasia. POEM, peroral endoscopic myotomy; CI, confidence interval.

Fig. 3. a Meta-analysis of the changes of the Eckardt score after POEM in geriatric patients with achalasia. **b** Meta-analysis of the changes of LES pressure after POEM in geriatric patients with achalasia. POEM, peroral endoscopic myotomy; LES, lower esophageal sphincter; MD, mean difference; SD, standard deviation.

events rate related to POEM was 9.0% and the clinical reflux rate was 17.4%.

The standard POEM procedure was generally performed as follows: (1) submucosal injection and mucosal incision, (2) submucosal tunneling, (3) myotomy, and (4) mucosal entry closure. But for geriatric patients, there are several challenges to perform the procedure. First, it has been reported that the anatomical structure of the esophagus changes with age, including increased nonpropulsive peristaltic contraction, esophageal dilation, and the increase in tertiary contraction resulting in corkscrew esophagus [14]. This could explain why we included studies reporting 11.5–31.5% of geriatric patients with a sigmoid-shaped esophagus. In this anatomic condition, it would naturally increase the difficulty of operation. Second, geriatric patients tend to have a higher comorbidity burden and reduced physiologic reserve, which led a higher risk of surgical anesthesia [33, 34]. What is more, if geriatric patients have received other treatment modalities before POEM, it often results in submucous fibrosis, which increases the difficulty of POEM [35, 36]. In our included studies, there were 42.0% (134/319) geriatric patients receiving previous interventions before POEM. Therefore, the

procedure in the geriatric population with these situations should be noted and required experienced endoscopists to operate.

In terms of efficacy, our systematic review showed that the pooled technical success rate of POEM for geriatric patients was 98.1% and the pooled clinical success rate was 92.5%. Our results were similar to those of adults reported by Barbieri et al. [37] in 2015, which reported the technical and clinical success rates were 97% (95% CI, 94–98%) and 93% (95% CI, 90–95%), respectively.

With regard to safety, our study revealed that the pooled adverse events rate related to POEM was 9.0% in geriatric patients. Barbieri et al. reported the major adverse events (required medical or surgical interventions) occurred in 14% (95% CI, 11–17%) of adults [37]. In our involved studies, only Chen et al. and Abe et al., respectively, reported one adverse event was graded as severe, associated with a case of cardiac arrhythmia during the procedure [14, 18]. In addition, the occurrence of adverse events in geriatric patients may be related to a combination of factors, such as physiologic reserve reduced with age, a higher comorbidity burden, and the esophageal tissue changed with age. Overall, POEM is a safe treatment method for geriatric patients.

As for clinical reflux, it was noted in 17.4% of patients in our meta-analysis, which is comparable to adult data of POEM, the pooled rate of esophagitis was 13% (47/354; 95% CI, 10–17%) [37]. Compared to LHM + Dor fundoplication, Costantini et al. conducted a clinical research which showed that esophagitis was found in 37.4% of POEM and 15.2% of Dor fundoplication patients ($p < 0.05$) [38]. Furthermore, Aiolfi et al. performed a meta-analysis which revealed that post-POEM gastroesophageal reflux disease was significantly higher when comparing to LHM [39]. Although proton pump inhibitors could effectively manage clinical reflux after the POEM procedure, appropriate methods still need to develop to decrease the occurrence of post-operative clinical reflux. Interestingly, the fundoplication procedure after POEM reported recently by Inoue et al. could alleviate the clinical reflux rate [40]. In their study, they successfully added the fundoplication procedure after standard POEM and showed that the clinical process after this technical was safe without immediate or delayed complications. Therefore, it might be more beneficial to add the anti-reflux procedure after basic POEM in the future.

We acknowledged that our study had several limitations. First, we included patients ≥ 65 years in our study. But studies of Chen et al. [14] and Abe et al. [18] involved octogenarians, which seemed to exaggerate the outcome of adverse events because Abe et al. [18] reported that octogenarians had significantly more adverse events with respect to nonoctogenarians. Then, NIH assessment of the included articles showed that there was an overall fair quality of evidence in our study. However, it is essential to know that the 7 studies we included were not randomized controlled studies, with 2 studies being conference abstracts, which is a very limited level of proof. Furthermore, we have included all the literature of POEM for treatment of geriatric patients with achalasia. However, in adult cohorts' study, there could be a few geriatric patients who we did not catch in the analysis. In addition, the research of Klair et al. reported the POEM for esophageal dysmotility disorders, in which a small number of geriatric patients without achalasia cannot be excluded [17]. Finally, several studies also had missing information on POEM features, such as achalasia type, ASA scores, number of sigmoid-shaped esophagus, myotomy length, operative time, postoperative Eckardt score, and LES pressure, which did not allow us to carry out a more comprehensive analysis.

Conclusions

Our current study demonstrated that the POEM was an effective and safe technique for achalasia in geriatric patients. Randomized trials need to be conducted to further compare the efficacy and safety of POEM between geriatric and young patients in the future.

Statement of Ethics

Our research does not require IRB approval and written consent as no human or animal subjects were used.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Study conception and design: Xiaowei Tang. Drafting of the manuscript: Chunyu Zhong, Shu Huang, and Huifang Xia. Acquisition of data and critical revision: Shali Tan, Muhan Lü, and Yan Peng. Revision of the manuscript and final approval of the manuscript: Xiaowei Tang.

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