Outcomes of Per-Oral Endoscopic Myotomy in the Treatment of Esophageal Achalasia: Over One Hundred Cases in a Single Tertiary Center

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ABSTRACT

Objective: To study the outcomes and complications of per-oral endoscopic myotomy (POEM) in patients with esophageal achalasia.

Materials and Methods: This retrospective observational study reviewed the medical records of esophageal achalasia patients who underwent POEM between March 2013 and September 2022. One hundred and eight cases were included.

Results: A total of 108 consecutive patients were included in this study and classified into 4 groups: 30 (27.8%) as type I; 53 (49.1%) as type II; 5 (4.6%) as type III; and 20 (18.5%) as unspecified due to unsuccessful catheter placement across the esophagogastric junction. The mean patient age was 46.10±16.59, 77 (71.3%) patients were female. Ten (9.3%) of the patients had undergone prior treatment, including balloon dilation, POEM, Heller myotomy, and nitroglycerine. Technical success was achieved in 106 (98.1%) cases, clinical success was evaluated only in 88 patients who follow up more than 6 month and the median follow-up time was 20.50 months (range 6-110 months). The clinical success was accomplished in 82 (93.2%), and 26 (24.1%) patients experienced perioperative complications which were significantly associated with anterior myotomy and probably operator learning curve. One patient (1.1%) had recurrent symptoms at 24-month follow up. Gastroesophageal reflux disease (GERD) was found in 19 (21.6%) patients, all of whom responded well to proton pump inhibitors (PPIs).

Conclusion: POEM is effective and safe in long-term treatment of achalasia. Although the incidence of symptomatic GERD was slightly high, the cases were not severe and were well controlled with medication.

Keywords: Per-oral esophageal myotomy; POEM; achalasia; outcomes; complication. (Siriraj Med J 2023; 75: 629-637)

INTRODUCTION

Esophageal achalasia is an esophageal motility disorder characterized by incomplete relaxation of the lower esophageal sphincter (LES), increased LES pressure and lack of normal peristalsis of the esophagus causing symptoms of dysphagia, chest pain, regurgitation and weight loss. Diagnosis and pre-operative evaluations include esophagogastroduodenoscopy (EGD), high-resolution esophageal manometry (HREM) and barium/time-barium esophagography (BE/TBE). Various treatments are available for lowering LES pressure, such as nitroglycerine, balloon dilation, and botulinum toxin injection, Heller myotomy and also per-oral endoscopic myotomy (POEM), which was first performed in 2008 by Professor Haruhiro Inoue, who later published his first case series of 17 patients in 2010.[1] Since then, many

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POEM studies, including retrospective single- and multi-center reviews, systematic reviews and meta-analyses, have reported its good clinical outcomes and safety.[2-7]

Our center first performed POEM in March 2013 and had conducted 108 of these operations by September 2022. In the early period, all procedures were performed by two experienced endoscopists, who later supervised operations conducted by a further 2 experienced endoscopists. This retrospective observational study aims to analyze the outcomes of our 9-year experience in a single tertiary center in terms of technical and clinical success, as well as perioperative and long-term complications, such as gastroesophageal reflux disease (GERD).

MATERIALS AND METHODS

This study was approved by Institutional Review Board (code: 66054). Medical records were retrospectively reviewed of 108 patients who underwent POEM between March 2013 and September 2022. The study included patients who had undergone the procedure after being diagnosed with achalasia from EGD, BE/TBE and/or HREM results.[8-12] The exclusion criteria were factors which identified individuals as unsuitable candidates for POEM, such as those with end-stage achalasia with massive dilated and tortuous esophagus; severe heart or pulmonary disease; coagulopathy; cirrhosis with portal hypertension; and history of previous endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), or radiofrequency ablation (RFA) of esophagus.[13,14]

The data used for pre-operative evaluation included gender, age, duration of symptoms, prior treatment, pre-operative Eckardt score, barium column height and width recorded at 5 minutes post-swallow from TBE, and integrated relaxation pressure (IRP) from HREM. Achalasia patients were classified into 4 groups: types I, II and III (by manometric patterns characterized with the Chicago Classification), and an unspecified group (patients whose esophageal manometry failed due to unsuccessful catheter placement across the esophagogastric junction). Further subtypes were classified as non-sigmoid and sigmoid type based on BE/TBE findings.

The procedure began with EGD for esophageal irrigation to eliminate the contents of the esophagus. Mucosal injection and incision were performed to create a submucosal tunnel appropriate for the myotomy technique and planned approach. Two different myotomy approaches were used in our department: anterior, in which the myotomy is performed at 12-1 o'clock; and posterior, at 5-6 o'clock. The choice of operative technique varied in accordance with operator preference or whether a previous myotomy by POEM or Heller technique had been performed, in which case the opposite approach was utilized. The length of myotomy in the esophagus varied according to the type of achalasia and manometry patterns, plus 2-3 cm in the gastric site. At the end of the procedure, the mucosal incision was closed with clips.[1]

Technical success was defined as complete performance of all steps.[15] Perioperative complications such as hypercarbia, pneumoperitoneum, subcutaneous emphysema, pneumothorax, pleural effusion, mucosal injury, perforation, or bleeding, were recorded. EGD with or without esophagogram was performed the following morning. If all mucosal clips were correctly placed and no leakage was observed, then the patients were allowed a clear liquid diet followed by a full liquid diet on the following day. The patients were discharged when they could tolerate a liquid diet, and they were advised to resume a soft diet the following week.

Postoperative clinical evaluation was performed using Eckardt score at 1, 3, and 6 months, and then once annually.[15] A score of over 3 within 6 months indicated clinical failure, while this score after 6 months was classified as recurrence.[16] Testing of HREM and TBE was performed in some patients who had questionable clinical evaluation but no time specific. GERD as a long-term complication was recorded if patients presented with reflux symptoms which were relieved by taking proton pump inhibitors (PPI) or when the results of 24 hours of pH monitoring confirmed acid exposure with pH levels below 4 for over 80 minutes/day or when EGD showed evidence of reflux esophagitis or Barrett's esophagus.[17]

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc. Chicago IL, USA), Descriptive statistics were used to characterize populations, categorical variables were presented as number and percentage, and continuous variables were represented by mean ± standard deviation (SD) or median (range) when the data are skewed. Differences in qualitative variables between two groups were analyzed using Chi-squared test or Fisher's exact test, while either Student's t-test or Mann-Whitney U test was used to compare continuous variables between two groups. Multivariate analysis was performed with logistic regression model in the "Enter" method.[18] Adjusted by surgical technique and subtype of achalasia and a p-value less than 0.05 was considered to be statistically significant.

RESULTS

A total of 108 consecutive patients underwent POEM. Their mean age was 46.10±16.59 years, and the majority were female (77/108, 71.3%). Twenty-nine (26.9%) had

underlying diseases such as hypertension, diabetes mellitus, reactive airway disease (asthma/COPD), hyperthyroid, cardiac arrhythmia (atrial fibrillation, sinus bradycardia, PVC), and others. All conditions were well controlled preoperatively. Thirty patients (27.8%) had achalasia type I, 53 (49.1%) had type II, 5 (4.6%) were type III, and 20 (18.5%) were unspecified type. With regard to subtype classification, 14 (13.0%) were sigmoid and 94 (87.0%) were non-sigmoid type. Median duration of symptoms was 12 months (range 2-240 months). Ninety-eight (90.7%) had had no prior treatment, while 10 patients (9.3%) had undergone previous modalities (2 pneumatic balloon dilations, 5 POEMs (3 POEMs from our hospital who were clinical failure from the first POEMs and 2 POEMs from outside hospital), 1 laparoscopic Heller myotomy, 1 open Heller myotomy, and 1 nitroglycerine). Median Eckardt score was 6 (range 0-10), and median IRP was 31.4 (range 11.5-83.6) mmHg. Preoperative TBE was conducted in 26 patients (24.07%) with median barium height 129.3 (range 34.6-242.7) mm, and median width 36.7 (range 22.8-76.4) mm as shown in Table 1.

With regard to surgical techniques and perioperative outcomes, about the myotomy technique, 26 patients (24.1%) underwent the myotomy technique using anterior approach and 80 patients (74.1%) had the posterior approach, while 2 patients' operative reports were missing (1.9%). Median myotomy length was 9 (range 2-17) cm, and median operative time was 120 minutes (range 45-295). Technical success was achieved in 106 patients (98.1%), while 2 patients (1.9%) had severe inflammation and fibrosis of esophageal mucosa resulting in failure to create a submucosal tunnel and, therefore, an unsuccessful operation. Perioperative complications occurred in 26 patients (24.1%) as follows: pneumoperitoneum needing intraoperative needle decompression (13), subcutaneous emphysema (4), pneumothorax (2), hypercarbia (4), perforation (2), mucosal injury (6), hypotension (1), hypoxia (1), pleural effusion (2) and bleeding (1). All complications were resolved with symptomatic and supportive treatment, except one case of pleural effusion, which required intercostal tube drain insertion. Median length of hospital stay was 9 days (range 4-41).

TABLE 1. Preoperative demographic and clinical characteristics of the study patients.

Characteristics	Total (n=108) n (%)
Gender	
Male	31 (28.7)
Female	77 (71.3)
Age (mean±SD)	46.10±16.59
Underlying Disease	
Yes	29 (26.9)
No	79 (73.1)
Type of achalasia	
Unspecified	20 (18.5)
Achalasia type I/II/III	30 (27.8)/ 53 (49.1)/ 5 (4.6)
Subtype of achalasia	
Non-sigmoid	94 (87.0)
Sigmoid	14 (13.0)
Duration of symptoms (month)	12 (2-240)
Prior treatment	
No	98 (90.7)
Yes	10 (9.3)
Pre-operative IRP (mmHg) (median (min-max))	31.4 (11.5-83.6)
Pre-operative Eckardt score	6 (0-10)
Pre-operative time barium swallowing	
Barium height at 5 min. (mm)	129.3 (34.6-242.7)
Barium width at 5 min. (mm)	36.7 (22.8-76.4)

Twenty patients (18.5%) were excluded from clinical outcomes due to follow up period less than 6 months, only the remaining 88 patients were evaluated in clinical outcomes. Median follow-up time was 20.50 months (range 6-110), median post-operative IRP decreased to 17.2 mmHg (range 0.7-73.5), median barium height fell to 30.0 mm (range 0.0-245.8), and median barium width went down to 24.8 (1.7-134.7) mm. Eighty-two patients (93.2%) had improvement of symptoms and Eckhardt score ≤ 3 and were classified as clinical successes, while 6 (6.8%) were categorized as clinical failures, as they developed symptoms and had Eckhardt score > 3 within 6 months. Three of these patients underwent laparoscopic Heller myotomy, while another 3 received POEM (which were included in the analysis as 3 patients who had prior treatment by POEM), and all 6 eventually achieved clinical improvement. Nineteen patients (21.6%) developed GERD, and all of these improved with daily PPI use. One patient (1.1%) who developed symptoms at 24 months was classified as a case of recurrence and successfully underwent laparoscopic Heller myotomy.

According to very low number of technical failure, there was no factor associated with technical success (Table 2). The patients without perioperative complication achieved clinical success higher than the patients with perioperative complication significantly on univariate analysis (p=0.027) as shown in Table 3 but it was not necessary to perform multivariate analysis due to small number of clinical failure. The perioperative complications were significantly associated with the use of the anterior myotomy technique on uni-and multivariate analysis as shown in Table 4 and Table 5.

TABLE 2. Factors associate with technical success.

Characteristics	Technical success Success (n=106) n (%)	 Failure (n=2) n (%)	P-value
Gender			0.494
Male	30 (96.8)	1 (3.2)	
Female	76 (98.7)	1 (1.3)	
Age	46(16-88)	44(44-44)	0.191
Co-morbidities			0.467
Yes	28 (96.6)	1 (3.4)	
No	78 (98.7)	1 (1.3)	
Type of achalasia			0.078
Unspecified	18 (90.0)	2 (10.0)	
Type I	30 (100.0)	0 (0.0)	
Type II	53 (100.0)	0 (0.0)	
Type III	5 (100.0)	0 (0.0)	
Subtype of achalasia			0.244
Non-sigmoid	93 (98.9)	1 (1.1)	
Sigmoid	13 (92.9)	1 (7.1)	
Duration of symptoms (month)	12 (2-240)	126 (12-240)	0.545
Prior treatment			1.000
None	96 (98.0)	2 (2.0)	
Yes	10 (100.0)	0 (0.0)	
Pre-operative Eckard	6(0-10)	4.5 (1-8)	0.726
Complications (early postoperative)			1.000
Yes	26 (100.0)	0 (0.0)	
No	80 (97.6)	2 (2.4)	

*Values were represented as n (%), mean+SD and median (min-max). The p-value from independent samples t-test and chi-square test with significant at p<0.05

**Factors associated with technical success could not be computed in pre-operative IRP, pre-operative time barium swallowing, myotomy site, myotomy length because failure group data was missing.

TABLE 3. Factors associate with clinical success.

Characteristics	Clinical success		P-value
	Success (n=82) n (%)	Failure (n=6) n (%)	
Gender			0.665
Male	25 (96.2)	1 (3.8)	
Female	57 (91.9)	5 (8.1)	
Age	47.2±16.96	45.5±2.81	0.444
Co-morbidities			0.339
Yes	21 (87.5)	3 (12.5)	
No	61 (95.3)	3 (4.7)	
Type of achalasia			0.808
Unspecified	17 (89.5)	2 (10.5)	
Type I	22 (95.7)	1 (4.3)	
Type II	39 (92.9)	3 (7.1)	
Type III	4 (100.0)	0 (0.0)	
Subtype of achalasia			1.000
Non-sigmoid	70 (93.3)	5 (6.7)	
Sigmoid	12 (92.3)	1 (7.7)	
Duration of symptoms (month)	12.5 (2-240)	33 (12-240)	0.309
Prior treatment			1.000
None	72 (92.3)	6 (7.7)	
Yes	8 (100.0)	0 (0.0)	
Pre-operative IRP	33.35±15.63	51.25±4.88	0.115
Pre-operative Eckard	6.11±1.92	6.17±3.06	0.947
Myotomy length (cm)	8.99±2.47	8.75±0.96	0.850
Operative time	120 (50-295)	80 (60-120)	0.113
Complications (early postoperative)			0.027*
Yes	17 (81.0)	4 (19.0)	
No	65 (97.0)	2 (3.0)	

*Values were represented as n (%), mean+SD and median (min-max). The p-value from independent samples t-test and chi-square test with significant at $p<0.05$

TABLE 4. Factors associate with complications.

Characteristics	Complications		P-value
	Yes (n=26) n (%)	No (n=82) n (%)	
Gender			0.818
Male	7 (22.6)	24 (77.4)	
Female	19 (24.7)	58 (75.3)	
Age	46.04±14.62	46.12±17.26	0.982
Co-morbidities			0.125
Yes	10 (34.5)	19 (65.5)	
No	16 (20.3)	63 (79.7)	
Type of achalasia			0.870
Unspecified	4 (20.0)	16 (80.0)	
Type I	6 (20.0)	24 (80.0)	
Type II	15 (28.3)	38 (71.7)	
Type III	1 (20.0)	4 (80.0)	
Subtype of achalasia			0.511
Non-sigmoid	24 (25.5)	70 (74.5)	
Sigmoid	2 (14.3)	12 (85.7)	
Duration of symptoms (month)	19(4-156)	12(2-240)	0.448
Prior treatment			0.696
None	25 (26.0)	71 (74.0)	
Yes	8 (80.0)	2 (20.0)	
Pre-operative IRP	33.42±15.88	32.68±15.09	0.861
Pre-operative Eckard	6.08±2.19	6.07±1.88	0.993
Pre-operative time barium swallowing			
Barium high (mm)	178.7(87.3-242.7)	120.8(34.6-235.3)	0.088
Barium wide (mm)	35.0(29.7-51.4)	38.6(22.8-76.4)	0.377
Technique			0.001*
Anterior approach	13 (50.0)	13 (50.0)	
Posterior approach	13 (16.3)	67 (83.8)	
Myotomy length (cm)	9.71±2.44	8.92±2.29	0.152
Operative time (min.)	120 (60-150)	120 (45-295)	0.688
LOS (days)	9 (4-15)	9 (5-41)	0.893

*Values were represented as n (%), mean+SD and median (min-max). The p-value from independent samples t-test and chi-square test with significant at $p<0.05$

TABLE 5. Multivariate analysis of factors associated with Complication.

Factors	Crude OR	95% CI	P-value	Adj. OR	95%CI	P-value
Surgical technique						
(Anterior approach)	5.154	1.951-13.616	0.001	5.194	1.955-13.798	0.001
(Posterior approach)	1			1		

On multivariable analysis by logistic regression model in the "Enter" method. Adjusted by Surgical technique and Subtype of achalasia, *significance at p<0.05.

DISCUSSION

After the excellent outcomes of the first POEM case series were reported by Professor Inoue in 2010[1], this procedure became accepted as a good treatment choice for achalasia. In our institute, 108 consecutive cases have been carried out with a good technical success rate of 106/108 (98.1%). The two technical failures, resulting from severe submucosal fibrosis, were unspecified type, one sigmoid and one non-sigmoid subtype. A recently published retrospective review showed that the majority of cases of submucosal fibrosis occur in type I achalasia and proposed a double tunnel method to effectively and safely reduce technical failure during POEM, improving the technical success rate from 68.3% to 98.4%.[19]

The short-term clinical success rate at 6-month follow up was 82/88(93.2%) patients. There was only one incidence of recurrence which was identified at the 24-month long-term follow up. At the maximum follow-up time of 110 months, the long-term clinical success rate was 92.0%, similar to the findings of two previous systematic reviews, one of which reported clinical success rates at 6-12 months, at 24 months, and at 36 months of 93.2%, 91.5% and 93.1% respectively.[7] The other review found pooled clinical success at 30 to 60 months and >60 months of 87% and 84% respectively.[6] This suggests that POEM is an effective treatment which yields very good results that can be maintained beyond 5 years.

Concerning about achalasia patients diagnosed despite normal IRP and outcome of treatment, Sanagapalli et al.[20] suggested that, to diagnosed a subset of achalasia patients with normal IRP, but impaired LES relaxation can demonstrated by additional provocative tests using rapid drink challenge (RDC), solid swallows during HREM, and/or barium esophagogram, and the outcome of treatment exhibited equivalent to achalasia diagnosed in the conventional fashion. There are 5 patients demonstrated normal IRP in this study, one patient loss follow up and 4 patients had clinical success with a 9-103 month- follow up period.

Even though the median of post-POEM IRP was higher than 15 mmHg (17.2 mmHg) but Eckardt score was lower than 3 can be explained by a multicenter, observational cohort study reported by Hata Y et al.[21] studied the associations between post-POEM HREM and the outcomes of POEM. 7% (151 of 2,171 patients) showed residual high post-POEM IRP (≥ 26 mmHg; Starlet [Starmedical Ltd, Tokyo, Japan]) still have comparable clinical outcome with low post-POEM IRP patients. The high pre-POEM IRP and gastric myotomy of ≤ 2 cm were predictive of residual of high post POEM IRP values, and a residual high post-POEM IRP not necessarily mean clinical failure and routine HREM follow-up is not recommended after POEM.

Another factor which may influence the outcome was "prior treatment". A retrospectively study reported the effect of prior treatment on clinical outcomes with a low rate of major adverse events but increase the risk of clinical failure after POEM.[22] In this study, 8 of 10 patients with prior treatment (5 POEM, 2 heller myotomy and 1 nitroglycerine) had minor perioperative complication but not statistically significant (p=0.696) and there was no technical failure and clinical failure in this group which probably due to small number of patients.

Regarding perioperative complications associated with myotomy techniques and practices used in our center, we performed POEM using the anterior approach in the first 16 cases routinely, and then moved on to the posterior approach which was then adopted as the normal technique, where technically feasible, over the next 3 years. Adverse events occurred in a total of 26 cases (24.1%), half of which resulted from use of the anterior approach, 13/26 cases (50.0%) and the majority of these (10) occurred in the first 16 cases. A randomized pilot study and a narrative review supported the correlation between anterior myotomy and increased risk of mucosal injuries due to its need for greater scope tip angulation[23,24], but the majority of findings of randomized clinical trials and systematic reviews have reported comparable outcomes

for the two approaches.[25-27] In our study, the significant complications from anterior approach might be from early period of learning curve.[28] The minimum threshold number of cases required for an expert interventional endoscopist to reach this plateau was around 13. Another study focusing on training 4 surgeons in the use of POEM found that the number of operations required to reach this plateau was 12 cases, after which significant reductions in dissection speed and perforation were achieved.[29]

GERD occurred in 19 of 88 patients (21.6%), all of whom were in the clinical success group. Some studies have claimed that the posterior approach probably has a higher incidence of GERD because it involves severance of both the circular and sling or oblique fiber, but the difference has been found to be of only borderline significance in some systematic reviews and meta-analysis.[30] In our study, the incidence of GERD was also higher with the posterior (15/67, 22.4%) compared to the anterior approach (4/21, 19.0%), but this difference was also not significant (p=1.00).

Limitation of this study was retrospective study and the small number of patients.

CONCLUSION

POEM is effective and safe as a long-term treatment for achalasia. While perioperative adverse events were associated with anterior myotomy and probably surgeons' insufficient experience in the use of the technique, these complications responded well to conservative management. Although the incidence of symptomatic GERD was slightly high at 21%, the cases were not severe and were successfully treated with to PPI.

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