Prospective evaluation of the efficacy of peroral endoscopic myotomy in patients with achalasia

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Abstract
Peroral endoscopic myotomy (POEM) is an endoscopic alternative to surgical myotomy in patients with achalasia. This study aimed to evaluate the efficacy and clinical outcomes of POEM.

A total of 20 patients with achalasia who underwent POEM between October 2016 and November 2017 were prospectively recruited. The intraoperative esophagogastric junction distensibility index (mm\(^2\)/mm Hg) was measured pre- and post-myotomy using an endoluminal functional lumen imaging probe. Clinical response was defined as Eckardt score $\leq$ 3. Health-related quality of life was measured by the 36-item short-form health survey score.

POEM was successfully completed in all cases. The median procedure time was 68.5 minutes (range 50.0–120.0), and the median myotomy length was 13 cm (range 11–18). Major adverse events were encountered in 2 cases. Overall, clinical responses were observed in all patients during a median follow-up of 11.9 months (range 1.2–26.2). Postoperative esophagogastric junction distensibility index was significantly higher than baseline (from 1.3 [range 0.8–6.9] to 6.3 [range 25–19.2], $P < .001$). The median Eckardt scores were decreased after POEM (5 [range 2–11] to 1 [range 0–3], $P < .001$), and the 36-item short-form health survey score was also improved significantly after POEM (67.5 [range 34.5–93.9] to 85.7 [range 53.4–93.3], $P = .004$).

POEM is an effective treatment for achalasia, based on the improvement of both symptoms and objective measures.

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Abbreviations: EGJ = esophagogastric junction, EGJ-DI = esophagogastric junction distensibility index, FLIP = functional lumen imaging probe, LES = lower esophageal sphincter, POEM = peroral endoscopic myotomy, SF-36 = the 36-item short form health survey.

Keywords: achalasia, myotomy, symptom assessment

1. Introduction
Achalasia is chronic esophageal motility disorder characterized by absence of peristalsis and impaired lower esophageal sphincter (LES) relaxation.\textsuperscript{[1]} Impaired bolus transit and outflow obstruction at the esophagogastric junction (EGJ) cause the symptoms of achalasia, including progressive dysphagia, regurgitation of undigested food, chest pain, and weight loss.\textsuperscript{[1]} Currently available treatment options for achalasia include surgical myotomy and endoscopic methods, such as botulinum toxin injection, pneumatic dilation, and peroral endoscopic myotomy (POEM).\textsuperscript{[2,3]} These treatments relieve symptoms by reducing esophageal outflow obstruction and improving bolus transport across the EGJ.

POEM was introduced as an endoscopic alternative to surgical myotomy.\textsuperscript{[4]} In addition to being less invasive, POEM has the advantage of being able to adjust the length and orientation of the myotomy. Studies have shown that POEM is effective and safe in the treatment of achalasia.\textsuperscript{[5,6]} POEM is associated with few adverse events, and those that do occur are minor and usually do not require further interventions.\textsuperscript{[7]} Moreover, POEM significantly improved patients' quality of life.\textsuperscript{[8]}

Objective measurements are preferred to patient-reports of symptoms alone for estimating treatment response. However, symptom relief after myotomy does not always correlate perfectly with significant improvements in esophageal emptying.\textsuperscript{[9,10]} The endoluminal functional lumen imaging probe (FLIP) is a multidetector impedance planimetry system that provides real-time images of data on the distensibility and geometric changes of EGJ measured through resistance to volumetric distention.\textsuperscript{[11]} It has been reported that EGJ distensibility better predicts esophageal emptying and treatment response than LES pressure...
in patients with achalasia.\(^{12,13}\) In addition, distensibility index measured during the procedure may be a useful predictor of clinical response.\(^{14,15}\) In this study, we investigated the efficacy and clinical outcomes associated with POEM for treatment of achalasia. In addition, we aimed to evaluate the role of intraoperative EGJ distensibility index (EGJ-DI) using an endoluminal FLIP to guide optimal extent of myotomy and to predict clinical outcomes.

2. Methods

2.1. Study population

Patients who underwent POEM for achalasia between October 2016 and November 2017 were consecutively recruited. Inclusion criteria were as follows; underwent POEM as clinically indicated, able to provide informed consent, and aged >18 years. We excluded patients in whom the POEM procedure or general anesthesia were contraindicated. The diagnosis of achalasia was made by esophageal high-resolution manometry, and achalasia subtype was determined using the Chicago classification of esophageal motility disorders.\(^{16}\) Sigmoid esophagus was defined as a significantly dilated and tortuous esophagus with axis deviation on esophageogram.\(^{17}\) This was a single-center prospective study that was approved by the Institutional Review Board (trial number 2016-0999) and was registered on clinicaltrials.gov (NCT 02989883). Written informed consent was obtained from each participant.

2.2. POEM procedure and follow-up

POEM was performed by three experienced endoscopists (D.H. K., H.Y.J., and K.D.C) under general anesthesia. All procedures were performed using a high-definition endoscope fitted with transparent caps. Carbon dioxide was used for endoscopic insufflation. A mucosectomy was made with hook knife (KD-620LR, Olympus, Tokyo, Japan) in the 5 to 6 o’clock position on the posterior wall of the esophagus after submucosal injection. A submucosal tunnel was created and extended down below the LES onto the gastric cardia with an insulated tip knife (IT knife nano, KD-612L/U, Olympus). Selective circular muscle myotomy of the inner circular muscle bundles was performed using a hook knife, starting 2 cm distal to the mucosal entry point and extending 2 to 3 cm toward the stomach. After FLIP measurement and confirmation of smooth passage of scope through the EGJ, the mucosal entry was closed using clips. Any mucosal injuries or perforations were also clipped, and hemostasis was performed using coagulation forceps (Coagrasper, FD-411QR, Olympus).

The EGJ-DI was measured intraoperatively before creation of the mucosal entry and after completion of myotomy using endoluminal FLIP (EndoFLIP, Crospion Ltd, Galway, Ireland). Under endoscopic visualization, the probe was introduced transorally to the esophagus and positioned across the EGJ. Cross-sectional areas and the corresponding intrabag pressure were measured using the balloon inflated to 40- and 50-mL volume. EGJ distensibility was assessed using the median value over a 30-second dynamic measurement of the narrowest cross-sectional areas corresponding to the EGJ and the median intrabag pressure, expressed in mm\(^2/\)mm Hg.

On discharge, patients were scheduled for a follow-up visit at 1 month, 3 to 6 months, and 6 to 12 months after POEM, and then yearly. Pre- and post-operative evaluations included endoscopy, high-resolution manometry, esophagography, esophageal transit scintigraphy, and endoscopic ultrasonography. Symptom scores including the Eckardt score and health related quality of life (HRQL) scores were obtained at baseline and at each clinic visit. Esophageal transit scintigraphy was performed while the patients were sitting in front of the collimator of the gamma camera. All patients were given the egg sandwich labeled with 1 mCi (37 MBq) Tc-99 m diethylene triamine pentaacetate (\(^{99m}\)Tc-DTPA). Dynamic images during the first 20 minutes were acquired using a gamma camera with a large field-of-view (Symbia Evo Excel or Intevo 16, Siemens Healthcare, Germany) equipped with a low energy, high-resolution collimator. Regions of interest were outlined on the esophagus and the stomach, and the time-activity curves were created. From these time-activity curves, percent esophageal retention measures at 1-, 5-, 10-, 15-, and 20 minutes were calculated.

2.3. Outcome parameters and definitions

The primary outcome was clinical success, as defined by post-POEM Eckardt score ≤3 at the last available follow-up visit. Secondary outcome measurements include adverse events, changes in EGJ-DI, and patients’ quality of life.

Symptoms after POEM were assessed using the Eckardt score and compared with preoperative data. The Eckardt score is the sum of the symptom scores for dysphagia, regurgitation, chest pain (0 point, absent; 1 point, occasional; 2 points, daily; 3 points, each meal), and weight loss (0, no weight loss; 1 point, <5 kg; 2 points, 5–10 kg; 3 points, >10 kg), resulting in a total score that ranges from 0 to 12, with higher scores indicating more severe disease.\(^{18}\) HRQL was measured using the 36-item short-form health survey (SF-36) questionnaire.\(^{19}\) The SF-36 assesses eight health care domains including general health, bodily pain, social functioning, emotional well-being, energy, and/or fatigue, role limitations because of emotional problems, role limitations because of physical health, and physical functioning. Every domain is scored from 0 to 100, with a higher number indicating a better-perceived quality of life. The physical and mental component summaries were further calculated based on the item scores using recommended procedures.\(^{20}\)

We defined major adverse event as an event that required additional and unplanned interventions or prolongation of a hospital stay.\(^{21,22}\) Bleeding was considered serious if prolonged endoscopic hemostasis or transfusion were required. Any defects of the mucosal layer overlying the artificially created submucosal tunnel, which could be managed with endoscopic closure, were considered minor adverse events. By contrast, mucosal defects, which could not be closed endoscopically and required other interventions were defined as major adverse events. Symptoms or signs related to air leakage were not regarded as adverse events unless additional interventions were needed to relieve symptoms.

Endoscopic findings of reflux esophagitis were defined using the Los Angeles classification system.\(^{23}\) Symptomatic gastroesophageal reflux was assessed using the Gastroesophageal Reflux Questionnaire, and a score ≥8 (a total score ranging from 0 to 18) was considered indicative of gastroesophageal reflux.\(^{24}\)

2.4. Statistical analysis

Procedural characteristics and clinical outcomes were assessed using prospectively collected data. Descriptive statistics for categorical variables are summarized by using proportions, and
those for continuous variables are summarized using medians and ranges. Paired variables, in the same patient, obtained before and after treatment were compared using Wilcoxon’s signed rank test. All reported P values were 2 tailed, and a value of 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 23.0 (IBM Corporation, Somers, NY).

3. Results

3.1. Patients characteristics

Baseline characteristics of study patients are summarized in Table 1. The median age of the 20 patients was 43 years (range 24–82) and 13 patients (65%) were female. The median symptom duration was 2.5 years (range 0.2–13.0). The median LES pressure and integrated relaxation pressure were 34.3 mm Hg (range 8.7–82.0) and 29.0 mm Hg (4.0–74.0), respectively, on esophageal high-resolution manometry. In terms of achalasia subtype, 8 patients (40.0%) had type I, 8 (45.0%) had type II, and 3 (15.0%) had type III achalasia. Esophagogram revealed sigmoid esophagus in 5 patients (25.0%). Six patients underwent endoscopic therapy, which included pneumatic dilation or botulinum toxin injection before POEM.

3.2. Procedure-related outcomes

POEM was successfully completed in all patients (100%) with a median procedure time of 68.5 minutes (range 50.0–120.0) (Table 2). EGJ-DI was assessed in all except 1 case; mucosal damage occurred while advancing the FLIP catheter after myotomy, and postoperative EGJ-DI was, therefore, unable to be measured in one patient. EGJ distensibility was significantly improved after treatment (Table 3 and Fig. 1). The median EGJ-DI at 40 mL was 1.3 mm²/mm Hg (range 0.8–6.9) before treatment compared with 6.3 mm²/mm Hg (range 2.5–19.2) after treatment (P < .001). Based on esophageal transit scintigraphy, percent clearance was remarkably increased after treatment.

Two patients had procedure-related major adverse events. Of these, one case of bleeding required drainage. The patient presented with orthostatic hypotension and tachycardia after the procedure, and a computed tomography scan of the chest revealed a submucosal tunnel hematoma and hemothorax. A chest tube was inserted and removed after 19 days of drainage. Another case of bleeding occurred during the myotomy secondary to a perforating artery. The bleeding focus was identified and controlled endoscopically using fibrin glue injection and coagulation forceps during the procedure.

With respect to minor adverse events, 2 mucosal tears were encountered and successfully closed by endoclips. Patients with air leakage, including 1 patient with subcutaneous emphysema and 8 patients with pneumomediastinum or pneumoperitoneum, did not show any clinically significant signs or symptoms. The median duration of hospital stay was 5.5 days (range 4.0–23.0).

At the follow-up endoscopic examination, reflux esophagitis was observed in 3 patients (15.0%), and all patients demonstrated grade B esophagitis. Reflux-related symptoms were reported in 11 patients (55.0%) and were relieved satisfactorily following proton pump inhibitor therapy.

### Table 1: Baseline characteristics of the patients.

| Characteristic                        | Value       |
|--------------------------------------|-------------|
| Number of patients                   | 20          |
| Age (yr)                             | 43 (24–82)  |
| Male                                 | 7 (35.0%)   |
| Achalasia subtypes                   |             |
| Type I                               | 8 (40.0%)   |
| Type II                              | 8 (45.0%)   |
| Type III                             | 3 (15.0%)   |
| Sigmoid esophagus                    | 5 (25.0%)   |
| Presenting symptoms                  |             |
| Dysphagia                            | 16 (80.0%)  |
| Chest pain                           | 1 (5.0%)    |
| Regurgitation                        | 3 (15.0%)   |
| Duration of symptoms (yr)            | 2.5 (0.2–13.0) |
| Eckardt score (scale 0–12)           | 5 (2–11)    |
| Previous treatment                   |             |
| Pneumatic balloon dilation           | 5 (25.0%)   |
| Botulinum toxin injection            | 1 (5.0%)    |

Data are shown as median (range) or number (%).

### Table 2: Procedural characteristics and outcome.

| Characteristic                        | Pre-POEM     | Post-POEM    | P value |
|--------------------------------------|--------------|--------------|---------|
| Procedure time (min)                 | 68.5 (50.0–120.0) | 13 (11–18)  |         |
| Myotomy length (cm)                  | 13 (11–18)   | 20 (100.0%)  |         |
| Adverse event                        |              |              |         |
| Bleeding                             | 2 (10.0%)    |              |         |
| Mucosal tear                         | 2 (10.0%)    |              |         |
| Hospital stays (d)                   | 5.5 (4.0–23.0)| 11.9 (1.2–26.2)| | |
| Follow up (mo)                       |              |              |         |
| Gastroesophageal reflux              |              |              |         |
| Erosive esophagitis                  | 3 (15.0%)    |              |         |
| Reflux symptom                       | 11 (55.0%)   |              |         |

Data are shown as median (range) or number (%).

### Table 3: Comparison of parameters pre- and post-procedure.

| Characteristic                        | Pre-POEM     | Post-POEM    | P value |
|--------------------------------------|--------------|--------------|---------|
| Eckardt score (scale 0–12)           | 5 (2–11)     | 1 (0–3)      | <.001   |
| Body mass index (kg/m²)              | 23.3 (15.5–27.3)| 25.5 (16.8–31.4)| <.001 |
| LESP (mm Hg)                         | 34.3 (8.7–82.0)| 18.0 (8.0–49.0)| <.003  |
| IRP (mm Hg)                          | 29.0 (4.0–74.0)| 14.5 (4.0–42.0)| <.003  |
| Intraoperative FLIP measurement (EGJ-DI, mm²/mm Hg) | 1.3 (0.8–6.9) | 6.3 (2.5–19.2) | <.001 |
| 40-mL distension                     |              |              |         |
| 50-mL distension                     |              |              |         |
| 40-mL distension                     | 1.3 (0.8–6.9) | 6.3 (2.5–19.2)| <.001  |
| 50-mL distension                     | 1.6 (0.5–5.0) | 5.0 (2.9–9.5) | <.001  |
| Esophageal scan (percent retention)  |              |              |         |
| 1 min                                 | 88.7 (6.5–99.5)| 15.3 (1.7–98.4)| .027   |
| 5 min                                 | 64.5 (2.9–99.0)| 4.6 (0.8–94.1)| .013   |
| 20 min                                | 61.6 (1.7–100.5)| 3.4 (0.5–87.5)| .010   |
| SF-36 score (n=18)                    | 67.5 (34.5–93.9)| 85.7 (53.4–93.3)| .004   |
| Physical division                    | 65.6 (43.1–93.8)| 83.7 (61.9–95.0)| .002   |
| Mental division                      | 64.6 (23.9–94.0)| 88.8 (44.9–100.0)| .004   |
| GerD2 score (n=16)                    | 7.5 (3–13)   | 6 (6–6)      | .070   |

Data are shown as median (range). EGJ-DI = esophagogastric junction distensibility index, FLIP = functional lumen imaging probe, GerD2 = the 36-item short-form health survey.
3.3. Clinical outcomes and quality of life

Overall, the clinical success rate for POEM was 100%. The median follow-up duration was 11.9 months (range 1.2–26.2). The Eckardt scores after POEM were available in 20 patients at 1 month and in 16 patients at 1 to 3 months and beyond. The mean Eckardt score was significantly decreased after the procedure and remained low during the follow-up period (Table 3 and Fig. 2). All patients gained weight after POEM: the median weight gain was 5.2 kg (range 0.4–14.8). Results of postoperative questionnaire revealed significant improvement in HRQL compared to baseline. In addition to total score, both the mental and physical component scores of the SF-36 improved significantly.

4. Discussion

In this study, we investigated the efficacy and clinical outcomes of POEM for treatment of achalasia. POEM achieved symptom relief, and therefore was clinically successful, in all patients. POEM was associated with significantly improved objective parameters of esophageal outflow obstruction, including LES pressure, esophageal emptying, and EGJ-DI. In addition, HRQL was improved after POEM.

Previously, it has been suggested that reducing the LES pressure to less than 10 mm Hg is a predictor of clinical response after pneumatic dilation for achalasia. However, many patients suffer from persistent symptoms even after achieving sufficiently low LES pressure, suggesting that LES pressure alone cannot predict clinical success. The FLIP measurement was introduced based on the speculation that EGJ distensibility, not LES pressure, could more determine LES opening and subsequent esophageal emptying. It provides useful information for estimating the optimal extent of myotomy during POEM and predicting treatment outcomes. FLIP estimates were correlated with symptoms as well as esophageal emptying, and patients with inadequate responses after treatment showed significantly lower EGJ-DI than those who experienced clinical successes. In addition, there were significant correlations between EGJ-DI and Eckardt score, integrated relaxation pressure, and bolus retention on timed barium esophagogram. In the present study, we also found that EGJ-DI significantly increased after successful POEM.

Sufficient myotomy from the esophageal body to the gastric side is key to successful outcomes. On the other hand, excessive myotomy should be avoided to minimize the risk of gastroesophageal reflux associated with increased EGJ distensibility. FLIP allows intraoperative assessment of EGJ-DI, facilitating determination of the adequacy of myotomy in real-time. Incremental myotomy can therefore be accomplished within a same session, optimizing the length of myotomy without compromising clinical outcomes. In addition to EGJ-DI, a recent study indicated that within-subject delta EGJ-DI was a more relevant and highly accurate predictor of clinical outcomes after pneumatic dilation. However, the normative value of FLIP parameters and the target range of EGJ-DI to achieve optimal treatment outcome have not been standardized. In the present study, we could not perform analyses based on EGJ-DI metrics to clarify the potential role of EGJ-DI as a predictor of clinical success, given that all patients achieved clinical success. Studies with large numbers of patients with various clinical outcomes are needed to clarify the role of EGJ-DI in optimizing the length of myotomy.

Various measurements were used for assessment of esophageal emptying in patients with achalasia. In addition to high-resolution impedance manometry, timed barium swallow test is a useful complementary tool that provides an intuitive assessment of esophageal bolus transit. Esophageal transit scintigraphy scans also allow quantitative assessment of bolus retention with much less radiation exposure than esophagogram. In a previous study, decreased radioisotope residue in the esophagus was found to be associated with favorable treatment
outcomes after pneumatic dilation. In the present study, we obtained esophageal transit scintigraphy scans before and after POEM and found that percent retention in the esophagus was significantly reduced after successful POEM. Although the association between improved esophageal emptying observed by scintigraphy scans and objective measures, such as LES pressure, EGJ-DI, and impedance manometry should be further clarified, scintigraphy scans may be useful for functional evaluation of esophageal emptying.

Our study had several limitations. First, we did not perform ambulator pH monitoring during follow-up, which could be useful to identify patients with pathologic reflux. Instead, all patients underwent endoscopic examination and completed symptom questionnaire. Second, our study cohort was relatively small, and potential selection bias and referral bias cannot be excluded. Another possible limitation of our study is that Eckardt score and SF-36 questionnaire can potentially produce recall and reporting biases. Despite these limitations, the validity of our findings is supported by strengths of this study, including its prospective design and inclusion of comprehensive and standardized follow-up assessments.

5. Conclusions

POEM is a feasible and effective treatment for patients with achalasia. In addition to symptom relief, POEM improved quality of life, as measured by the SF-36 questionnaire. FLIP measurements may be useful for objectively determining the adequacy of LES disruption and predicting treatment outcomes.

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