

The relationship between the interruption of the lower esophageal sphincter and relief of dysphagia after per-oral endoscopic myotomy for achalasia

Sheng Wang¹, Xiang Liu¹, Nan Ge¹, Guoxin Wang¹, Jintao Guo¹, Wen Liu¹, Jinlong Hu¹, Siyu Sun¹

¹Department of Gastroenterology, Shengjing Hospital of China Medical University, Shenyang, Liaoning Province, China

ABSTRACT

Background and Objectives: We investigated the relationship between the interruption of the muscularis propria of the lower esophageal sphincter (LES) measured by EUS and the relief of dysphagia in patients with esophageal achalasia treated by per-oral endoscopic myotomy (POEM). **Patients and Methods:** Patients with achalasia treated by POEM at our endoscopy center between January 2015 and August 2016 were included in the study. Preoperative clinical characteristics and dysphagia and Eckardt scores, operative and postoperative complications, dysphagia and Eckardt scores at 3- and 7-months postoperatively, and the incidence of postoperative gastroesophageal reflux disease (GERD) were recorded. Patients were divided into two groups according to the degree of separation of the muscularis propria at the LES, as measured by EUS: Group A, separation distance 2–5 mm and Group B, separation distance 5–9 mm, for comparison. **Results:** Preoperative clinical characteristics, Eckardt scores, and dysphagia scores were similar in the two groups. Patients in both groups had significant symptom relief postoperatively, with significant decreases in Eckardt scores and dysphagia scores. On the comparison between the groups, there was no significant difference in postoperative Eckardt score, but the dysphagia score was statistically significantly lower in Group B as compared to Group A ($P < 0.05$). There was no significant difference between the groups in the incidence of gas-related complications or in the incidence of postoperative GERD. **Conclusions:** POEM was largely effective in the treatment of esophageal achalasia in this study. Patients with larger defects of the muscularis propria at the LES after myotomy had greater relief of dysphagia without an increased incidence of postoperative complications.

Key words: achalasia, dysphagia, EUS, per-oral endoscopic myotomy

INTRODUCTION


Achalasia is a not uncommon disorder of esophageal motility of unclear etiology.^[1] It is characterized by impaired relaxation of the lower esophageal sphincter (LES) and weakness of esophageal peristalsis. The

characteristic symptoms include dysphagia, regurgitation, chest pain, nocturnal cough, and weight loss due to eating difficulties. There is no known cure for achalasia. Current

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Address for correspondence

Dr. Siyu Sun, Department of Gastroenterology, Shengjing Hospital of China Medical University, Sanhao Street 36, Shenyang 110004, Liaoning Province, China. E-mail: sun-siyu@163.com

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treatments include drug therapy, laparoscopic Heller myotomy (HM), and endoscopic treatment, including balloon dilatation, botulinum toxin injection, placement of retrievable metal stent, and per-oral endoscopic myotomy (POEM). POEM is a newer minimally invasive treatment with short-term efficacy^[2-4] that is comparable to that of HM, but with shorter operative time, reduced hospital stay, and lower incidence of postoperative complications.^[5] However, as an increasing number of patients are being treated by POEM, we are finding that not all of them are having meaning full symptom relief. As yet, there is no clear prognostic indicator for the efficacy of POEM. We hypothesized that the extent of interruption of the muscularis propria at the LES after myotomy, as measured by EUS, might be useful for predicting symptomatic relief. In this study, we retrospectively analyzed 29 patients with achalasia who were treated by POEM to examine the relationship between the interruption of the muscularis propria at the LES and relief of symptoms.

PATIENTS AND METHODS

This study was approved by the Institutional Review Board and Ethics Committee of China Medical University, and all patients signed written informed consent.

Patients

Patients who were treated in the endoscopy center at Shengjing Hospital of China Medical University from January 2015 to August 2016 were enrolled. The inclusion criteria were the diagnosis of achalasia confirmed by manometry and radiographic findings in patients with classic symptoms, including dysphagia, regurgitation, chest pain, and weight loss, that were unresponsive to drug therapy. Only patients who had not had any previous surgical or endoscopic intervention for achalasia were included.

Methods

Endoscopic instruments

Gastroscope (Pentax, Japan) with MD-47920 transparent cap, endoscopic injection needle (Boston Scientific, USA), KD-620 LR hook knife: 3M electric hemostatic clamp; ROCC-D-26 soft-tissue clips, and CR4500 carbon dioxide aspirator were used to perform POEM.

Procedure

Preoperative preparation

Patients fasted for 48 h before POEM and gastric decompression were performed 12 h before POEM

to suction gastric juice and residual food. We pulled the gastric tube into the esophagus (30 cm from the incisors) at 4 h preoperatively to remove residual esophageal food, and we removed the tube before the procedure. All patients received gastroscope-assisted esophageal lavage before the initiation of POEM.

Position and anesthesia

Patients were in a left lateral decubitus position, and POEM was performed under general endotracheal anesthesia with positive pressure ventilation.

Creation of the submucosal tunnel

First, submucosal injection of methylene blue saline solution (1:10000) was administered from a point in the posterior or lateral esophageal wall approximately 10 cm from the gastroesophageal junction (GEJ), and a longitudinal mucosal incision of approximately 1.5–2 cm was made at this point. During the procedure, we used electrocute 40 and electrocoagulation 50. The submucosal tunnel was then established from the point of incision, through the GEJ, and about 3 cm into the proximal stomach. We judged the passage through the GEJ by the disappearance of resistance, the opening of the visual field, and the changes in the submucosal vascular pattern, from a palisade pattern in the esophageal submucosa to a web pattern characteristic of the gastric submucosa.^[6,7] Pinpoint hemorrhage could be controlled by flush or by coagulation with the tip of the hook knife; hemostasis for larger vessels was performed with the electric hemostatic clamp [Figure 1a and b].

Myotomy

After the creation of the submucosal tunnel, we withdrew the gastroscope to a point approximately 3–5 cm distal to the mucosal incision to begin a full-thickness myotomy at approximately 5–7 cm above the GEJ. The myotomy was continued from this point to approximately 1–2 cm into the stomach. We used the tip of the hook knife or the electric hemostatic clamp for hemostasis [Figure 1c]. We performed full-thickness myotomy for all patients. Full-thickness myotomy is now known to have similar short-term results as inner circle myotomy, with a similar incidence of complications and the advantage of a shorter operative time.^[8]

Closure of the mucosal incision

After ensuring complete hemostasis and smooth passage of an endoscope into the gastric cardia, the mucosal

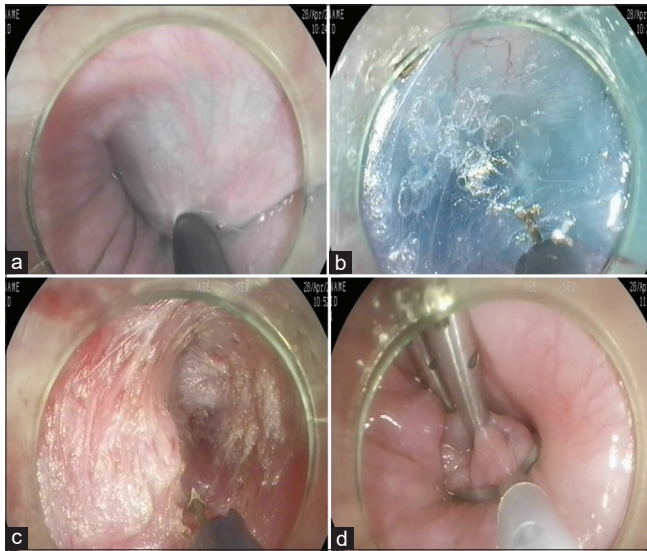


Figure 1. (a) The submucosal methylene blue saline solution (1:10000) is injected at the posterior or lateral esophageal wall approximately 10 cm from the gastroesophageal junction, and a mucosal longitudinal incision of approximately 1.5–2 cm is made at the injection site. (b) The submucosal tunnel is established. (c) The muscularis propria is divided. (d) The mucosal incision is closed in a straight line with hemostatic clips

incision was closed in a straight line (distal to proximal) with hemostatic clips [Figure 1d].

Postoperative care

Blood pressure, oxygen saturation, and electrocardiogram were monitored for 24 h, and patients remained fasting for 48 h and were observed for short-term effects and postoperative complications. If there was no perforation, subcutaneous emphysema, or mediastinal emphysema, a semi-liquid diet was started and was gradually advanced to a regular diet after 1 week.

Postoperative follow-up evaluation

EUS was performed 5–7 days after POEM to evaluate the wound healing, check for residual metal clips, examine the openness of the cardia after insufflation, the structure of the LES, and in particular, the interruption of the muscularis propria at the LES [Figure 2a and b]. The patients were then scheduled for 3-month, 7-month, and 1-year follow-up visits, with yearly visits afterward.

Data collection

General patient characteristics, including age, gender, and duration of achalasia were recorded. Eckardt scores were measured before POEM, at 3 days after POEM, and at the 3-month and 7-month follow-up assessments. The grading criteria for the Eckardt score are shown in Table 1. POEM was considered effective based

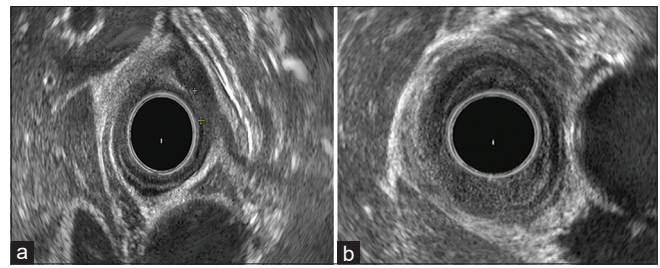


Figure 2. (a) The separation distance measured by EUS is 4 mm. (b) The distance measured by EUS is 7 mm

Table 1. Eckardt score

Score	Symptoms			
	Weight loss (kg)	Dysphagia	Poststernal pain	Regurgitation
0	No	No	No	No
1	<5	Occasional	Occasional	Occasional
2	5-10	Daily	Daily	Daily
3	>10	Each meal	Each meal	Each meal

The classification of achalasia is as follows: Level 0, score: 0-1; Level I, score=2 to 3; Level II, score=4 to 6; Level III, score >6

on postoperative Eckardt scores of ≤ 3 . Intra- and post-operative complications, including subcutaneous emphysema, mediastinal emphysema, pneumothorax, and pneumoperitoneum; procedure-related adverse events (bacteremia, infection in the submucosal tunnel, cardia tear, and delayed bleeding); and incidence of gastroesophageal reflux disease (GERD) after POEM were recorded. Follow-up was performed in person throughout the hospitalization period and at our center for the scheduled follow-up visits. We also followed-up with patients by telephone after they were discharged.

Statistical analysis

All statistical analyses were performed using the SPSS software version 17.0. Normally distributed data were evaluated by *t*-test and were described by mean \pm standard deviation; nonnormal data were described by mean value. The count data were analyzed by Chi-square test or Fisher's exact test. *P* < 0.05 for differences was considered statistically significant.

RESULTS

A total of 34 patients with achalasia were treated in the endoscopy center at the Shengjing Hospital of China Medical University from January 2015 to August 2016. Five patients were excluded from the present study; 1 because of severe lung disease and 4 with previous intervention for achalasia. Thus, a total of 29 patients, 11 men and 18 women, median age 52 years (range 23–78 years), were included.

The duration of symptoms ranged from 0.17 to 43 years, with a median of 7 years. The patients were divided into two groups based on the median size of the interruption in the muscularis propria after POEM. There were 19 patients with separation distances between 2 mm and 5 mm (Group A) and 10 patients with separation distances between 5 mm and 9 mm (Group B). General patient characteristics and preoperative Eckardt and dysphagia scores are shown in Table 2. There were no significant differences between the groups preoperatively.

POEM was successfully performed in all 29 patients. Overall, the Eckardt scores were significantly decreased at 3 days after the operation compared to preoperative Eckardt scores (7.76 ± 2.13 vs. 1.14 ± 1.15 , $P = 0$), confirming that the procedure was initially effective. During the follow-up period, 25 patients maintained a significant relief of dysphagia, whereas four patients did not have continued improvement of symptoms during the short-term and long-term follow-up. Two patients, one with preoperative Eckardt score of 10 points and the other with preoperative Eckardt score of 7 points, had Eckardt scores of 5 at 3 days after POEM without improvement of dysphagia scores. A third patient experienced progressive deterioration of dysphagia and weight loss from 2 months after treatment, with an Eckardt score of 6 points at the 3-month follow-up, and the fourth patient had the symptoms of dysphagia and regurgitation flux from 6 months after treatment, with an Eckardt score of 8 points at the 7-month follow-up. Preoperative and 3- and 7-month postoperative Eckardt scores for all patients are shown in Table 3.

The interruption of the muscularis propria measured at EUS for all patients ranged from 2 mm to 9 mm, with a mean value of 4.41 ± 2.06 mm. POEM was effective in 78.9% of the patients in Group A (separation distance 2 mm–5 mm) and in 100% in Group B (5 mm–9 mm) ($P > 0.05$). All four patients who had poor outcomes were in Group A, but the difference in efficacy between the two groups did not reach statistical significance.

Overall, postoperative symptom relief, particularly dysphagia, was significant in both groups [Tables 4 and 5]. There was no statistically significant difference in the Eckardt score between the two groups. (1.26 ± 0.93 vs. 0.6 ± 0.51 $P < 0.05$), but the dysphagia score was statistically significantly lower in Group B as compared to Group A (1.26 ± 0.93 vs. 0.6 ± 0.51 , $P < 0.05$) [Table 6].

Four patients (13.7%) experienced short-term subcutaneous emphysema, 3 in Group A and 1 in Group B; the difference in the incidence of gas-related complications between the two groups was not significant ($P = 1$), and the subcutaneous emphysema was spontaneously absorbed within 3–5 days postoperatively in all patients. Four patients (2 in Group A and 2 in Group B) developed reflux and heartburn, the classic symptoms of GERD, but there were no GERD-related abnormalities evidenced on gastroscopy, and there was no statistically significant difference in the incidence of GERD between the two groups ($P = 0.59$). There was no incidence of delayed bleeding, perforation, infection, or other adverse events.

DISCUSSION

POEM is a recent method for the treatment of esophageal motility disorders that was initially proposed by Inoue *et al.*^[9] and was first used for the treatment of achalasia. With advances in endoscopic equipment and in the skills of endoscopists, POEM is now widely recognized as an important choice for the treatment of achalasia. According to recent data,^[10] the success rate of POEM ranges from 94% to 100%, the incidence of postoperative adverse events ranges from 0% to 7%, and the short-term efficacy ranges from 82% to 100%. As yet, clinicians do not have a validated assessment tool or predictive indicator for determining which patients will have good results and which patients will have poor results necessitating further intervention.

At present, most researchers use the Eckardt score to evaluate the efficacy of POEM. Other commonly used

Table 2. Patient characteristics and preoperative Eckardt and dysphagia scores

General information	Total	Group A	Group B	P
Gender (male/female)	29	6/13	5/5	0.43
Median age (years, range)	52 (23-78)	52 (23-78)	51 (37-65)	0.60
Median duration of achalasia (years, range)	7.0 (0.17-43)	7.0 (0.75-43)	6.0 (0.17-30)	0.67
Preoperative Eckardt score	7.76±2.13	7.47±1.92	8.30±2.49	0.33
Preoperative dysphagia score	2.76	2.68	2.90	0.42

The comparison of preoperative dysphagia score used the rank-sum test

Table 3. Comparison of dysphagia score and Eckardt score at different time points

	Dysphagia score	Eckardt score
Preoperation (A)	2.75	7.76±2.13
Postoperative 3 months (B)	0.96	1.79±1.56
Postoperative 7 months (C)	1.03	1.97±1.93
<i>P</i> (A vs. B)	0	0
<i>P</i> (A vs. C)	0	0
<i>P</i> (B vs. C)	0.27	0.71

The comparison of preoperative dysphagia score used the rank-sum test

Table 4. Comparison of dysphagia score and Eckardt scores in Group A

Group A	Dysphagia score	Eckardt score
Preoperation	2.68	7.47±1.93
Postoperation	1.26	2.37±2.14
<i>P</i>	0	0

The comparison of preoperative dysphagia score used the rank-sum test

Table 5. Comparison of dysphagia score and Eckardt score in Group B

Group B	Dysphagia score	Eckardt score
Preoperation	2.90	8.30±2.49
Postoperation	0.60	1.20±1.22
<i>P</i>	0	0

The comparison of preoperative dysphagia score used the rank-sum test

Table 6. Comparison of dysphagia score and Eckardt score between the two groups

	Group A	Group B	<i>P</i>
Postoperative dysphagia score	1.26±0.93	0.60±0.51	0.048
Postoperative Eckardt score	2.37±0.03	1.2±0.88	0.12

t-test was used for this comparison

evaluation criteria include quality of life score, barium meal observation, esophageal diameter changes, and high-resolution esophageal manometry.^[11] All of these methods are useful to evaluate the efficacy of POEM, but they cannot predict the outcome of POEM. With current operative techniques, it is possible to adjust the length of the incision through the LES, but there is no way to control the width of the defect once the divided muscle tissues begin to contract. We hypothesized that the width of the defect could be related to clinical outcomes, and we used EUS, which is widely available, to measure the separation distance after the division of the LES to determine whether the relationship of this distance to the surgical outcome could predict the efficacy of POEM. EUS can quantitatively measure the interruption of the LES, which is clearly visible on the image as a partial defect in the annular muscular layer. We can determine the size of the defect at the LES and then examine its relationship to the extent of symptom relief and the incidence of complications.

Once the muscle is divided, the local digestive tract wall loses its peristaltic ability, and the range of the defect does not change with peristalsis, thus avoiding the effect of esophageal peristalsis on changes in esophageal pressure and esophageal diameter.

The operative success rate of POEM was 100% in our study, and the immediate effect was good. The improvement of symptoms after POEM was statistically significant. However, this immediate improvement may be related to intraoperative anesthesia and endoscopy, leading to relaxation of the LES, so the Eckardt score at this point is not representative of the true symptom improvement or the potential long-term efficacy. Significant decreases in the 3- and 7-month postoperative Eckardt and dysphagia scores in comparison to the preoperative scores in our cohort proved the effectiveness of POEM, and there was no significant difference between the short-term and long-term effects, which confirmed the stability of the operation. Nonetheless, because individual patients are different, the same treatment may have a different effect, as was demonstrated during the long-term follow-up in four patients who had recurrence or deterioration of symptoms, with increasing Eckardt scores verifying poor outcomes. The overall efficacy of POEM in our study was 86.2% (25 of 29 patients with good results), which is similar to the outcomes reported elsewhere.^[10]

The question of whether there is a way to predict postoperative efficacy, or whether there is a way to consistently ensure the effectiveness of POEM, remains. The size of the defect after the division of the muscularis propria may have an impact on the prognosis, and patients with wider defects seem to have greater symptom relief.^[6] Therefore, we examined the effects of different defect widths on the short-term and long-term efficacy of POEM. We measured the separation distance by EUS because it is an intuitive and accurate method that can provide quantitative measurements.^[12,13] As noted, we divided the patients into two groups based on the median widths of the defect in the muscularis propria at the LES, and we found that the patients with wider defects (5–9 mm, *n* = 10 *vs.* 2–5 mm, *n* = 19) had better outcomes in terms of symptom relief, although the difference did not reach significance and we, therefore, cannot conclude, based on this relatively small cohort, that the separation distance can affect the overall efficacy. POEM should prevent the cardia muscle from

completely impeding the passage of food and liquid, thereby relieving dysphagia, improving the patient's nutritional status, and preventing esophageal fluid retention and muscle spastic pain. In this study, in terms of improvement of the dysphagia score alone, outcomes in patients with larger myotomy defects were significantly better than in those with smaller defects. We think that the larger defect results in decreased contracture of the muscle tissues and makes approximation of the ends of the divided muscle more difficult, allowing for sustained relief of dysphagia. Indeed, in our study, the four patients who had poor symptomatic relief were all in Group A. Although EUS initially confirmed that the cardia muscles in these patients were disrupted by POEM, all of them had gradual return of symptoms to preoperative levels during the long-term follow-up. We think this may be because postoperative adhesions formed during the healing process cause approximation of the muscle ends. Although local muscle contraction would still be absent, the adhesions may create an annular constriction. Although we do not have definitive evidence to confirm this mechanism, our results did support the hypothesis that a wider myotomy has an advantage for the overall relief of the symptoms, particularly dysphagia, with a reduced incidence of recurrence. Some researchers have also noted that the efficacy of POEM is greater in young patients and in those with less severe symptoms.^[14,15] The pathogenesis of achalasia remains unclear, and there are many factors that may contribute to the remission of symptoms after POEM. Thus, the mechanism of symptomatic relief associated with larger intermittent distance of the muscularis propria must be confirmed by further research.

Four patients in our study (3 from Group A and 1 from Group B) had subcutaneous emphysema after POEM. We confirmed that this was not related to division of the muscle layer, and because we used CO₂ for insufflation, CO₂ was solved spontaneously within 3–5 days. No delayed bleeding, perforation, infection, or other adverse events occurred. Finally, during the follow-up, four patients, 2 from each group, developed typical symptoms of GERD. The incidence of GERD was not statistically different between the groups ($P = 0.59$). When the LES is divided, the anti-reflux mechanism of the cardia is decreased, but the structures around the esophagus, including the diaphragm and the diaphragmatic esophageal ligament, along with the angle of His and other anatomical

anti-reflux barriers remain intact, so that the majority of patients so far have had no or only mild symptoms GERD after POEM, which are usually relieved with proton-pump inhibitors. The finding that there was no significant difference in the incidence of gas-related or postoperative complications or of GERD between the two groups in our study indicates that a wider myotomy should not cause an increase in the risk of adverse events or any additional increase in the risk of GERD.

There were limitations in our study. First, you have not performed the pH manometry. We diagnosed GERD based on the patient's symptoms. Second, the sample size of this study is limited, and the results will have to be confirmed in a larger and more comprehensive controlled study to reach a more definite conclusion.

CONCLUSIONS

In summary, POEM was largely effective in the treatment of esophageal achalasia in this study. Patients with larger defects of the muscularis propria at the LES after myotomy had greater relief of dysphagia without the increased incidence of postoperative complications.

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Conflicts of interest

There are no conflicts of interest.

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