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Development and technique of per oral endoscopic myotomy (POEM) for achalasia

E. Rieder[1], C. M. Dunst[2], A. S. Kastenmeier[1], K. I. Makris[1], L. L. Swanström[2]

[1]Minimally Invasive Surgery Program, Legacy Health System, Portland, Oregon, USA
[2]Division of GI and Minimally Invasive Surgery, The Oregon Clinic, Portland, Oregon, USA

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Summary. *Background:* Achalasia is a primary esophageal motor disorder involving the absence of esophageal body peristalsis and defective relaxation of the lower esophageal sphincter. The optimal treatment is still controversial. Per oral endoscopic myotomy (POEM) has recently evolved from developments in Natural Orifice Translumenal Endoscopic Surgery (NOTES).

Methods: Substantial experimental work in animals and cadavers was performed to establish the technical approach for POEM before clinical implementation. This flexible endoscopic procedure involved incising the mid-esophageal mucosa followed by access into the submucosal space. A tunnel onto the gastric cardia was dissected and selective division of the circular/sling-fibers of the lower esophageal sphincter (LES) was performed by needle knife cautery. The mucosotomy was closed by conventional endoscopic hemoclips. Subsequently, a 61-year-old male patient with achalasia was enrolled in an ongoing study.

Results: Based on preclinical work, the steps of endoscopic submucosal myotomy were defined. In the patient described, mucosal balloon-dilatation facilitated access into the submucosal space. Dissection was performed until 3 cm below the gastroesophageal junction and the partial myotomy was 7 cm. The mucosal entry was easily closed. Postoperative esophagogram did not detect esophageal leakage and the patient was discharged on the next morning. He reported immediate symptom relief on the 2-week clinical follow-up without the need of pain medication.

Conclusions: POEM for achalasia is a perfect example of the true surgical revolution resulting from NOTES research. Although the long-term outcome of POEM has still to be evaluated, the promise of this novel procedure seems more than obvious.

Correspondence: Lee L. Swanström, MD, Clinical Professor of Surgery, Oregon Health & Science University (OHSU), Gastrointestinal and Minimally Invasive Surgery Division, The Oregon Clinic, 1040 NW 22nd Avenue, Suite 560, Portland, OR 97210, USA.
Fax: ++1 503 281 0575
E-mail: lswanstrom@orclinic.com

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Introduction

Achalasia is a primary esophageal motor disorder that is typically characterized by dysphagia, retrosternal pain, and regurgitation as well as accompanying weight loss. These four cardinal symptoms are also used to clinically score the severity of achalasia [1]. The etiology for the absence of esophageal body peristalsis together with the defective relaxation of the lower esophageal sphincter (LES), producing a functional obstruction at the gastro-esophageal junction (GEJ), is not fully understood. However, autoimmune reactions against the myoenteric (Auerbach's) plexus of the esophagus with loss of inhibitory nerves and unopposed cholinergic stimulation have been hypothesized [2]. Also genetic and infectious causes have been discussed. Described from infancy through the ninth decade of life, no association of gender or race has been found yet.

The primary goal of therapy is to provide relief of dysphagia, simultaneously preventing gastroesophageal reflux. However, as only few randomized controlled trials have tried to define the optimal therapeutic approach, treatment still varies widely. Endoscopic botulinum-toxin injection into the esophageal muscle layer at the LES inhibits the release of acetylcholine from nerve endings and thereby relaxes the muscles. Due to its easy and inexpensive application it appears appealing, but has a high failure rate and should be reserved for selected patients [3]. More disruptive methods focusing on the forced relaxation of the LES, such as pneumatic balloon-dilation or surgical esophagomyotomy, have been shown to be the most effective [4]. Although it has been shown that younger patients might benefit form primary myotomy [5], superiority between these two options is still a matter of discussion [3, 6].

First reported in 1914 [7], the surgical division of the distal esophageal muscle layer is now primarily

performed by laparoscopic techniques [8]. The laparoscopic era has certainly changed the treatment paradigm as well as its sequence for esophageal achalasia [9]. However, due to necessary dissection at the phrenoesophgeal ligaments, effective surgical division of the esophageal muscle layer also inevitably disrupts the anatomical integrity of the LES anatomy. This leads to the necessity of an anti-reflux procedure in the majority of patients, which is not without its own morbidity. Recent efforts in the development of Natural Orifice Translumenal Endoscopic Surgery (NOTES) led to the evolution of novel therapeutic options. Pasricha and colleagues initially described the feasibility of a pure flexible endoscopic esophageal myotomy in a survival animal model [10] using a submucosal flap technique [11]. Other investigators who used an esophageal mucosal flap have also evaluated this technique (full-thickness myotomy) together with a subsequent endolumenal fundoplication [12]. The first report in humans was from Inoue and colleagues [13]. This group also coined the term per-oral endoscopic myotomy (POEM) and reported excellent short-term results on their refined technique in 17 patients.

We report our preclinical development efforts and refinements we made, together with our current clinical approach used for POEM by means of a 61-year-old male suffering from esophageal achalasia, enrolled in a clinical study initiated in October 2010.

Methods

Development of flexible endoscopic myotomy

Based on substantial previous work in minimally invasive Heller myotomy [14] and more recent experimental as well as clinical efforts in NOTES [15], our group initiated a phase 1 animal and cadaver study on the use of flexible endoscopy for esophagomyotomy. Initially, to overcome the need for an esophagotomy a small cervical incision was used for mediastinal access [16] and subsequent dissection down to the GEJ. Complete anterior or posterior myotomy was shown to be feasible via this approach in ten pigs and two human cadavers [17].

In subsequent research the technique of POEM has been practiced extensively and has also been refined on a substantial number of acute and cadaveric animal models (unpublished data). The basic procedural steps for POEM involve endolumenal access for a standard flexible upper scope through a longitudinal esophageal mucosal incision. Once in the esophageal submucosal space, a tunnel is created by blunt and electrocautery dissection down to and below the LES. Subsequently, division of only the inner esophageal muscle layer is performed.

Similar to the technique used for a transgastric approach into the abdominal cavity in NOTES, balloon-dilatation for submucosal access after the mucosal incision has been evaluated and compared to pure blunt submucosal insertion of the endoscope. Several different techniques for dissection or for endoscopic division of esophageal muscle fibers, such as the use of novel endoscopic scissors (Fig. 1), were also evaluated in these experimental models. Different technical modalities for closure of the mucosotomy were also tested and included suturing devices and various clips.

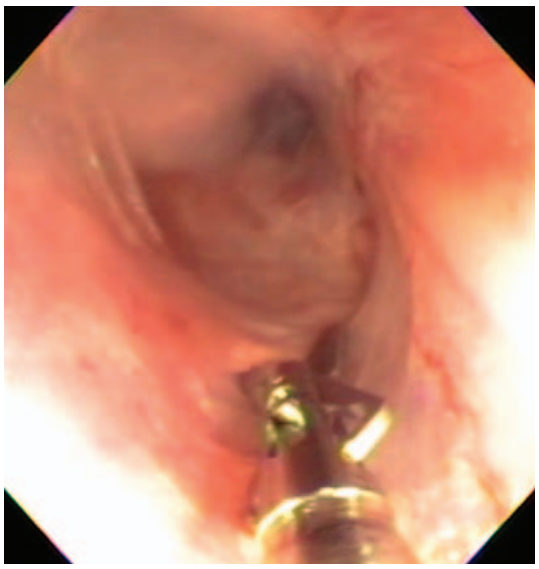

Fig. 1: In an animal model the endoscope was inserted into the submucosal space of the esophagus. Flexible endoscopic scissors were used for the submucosal myotomy (bottom). The esophageal mucosa is visible above

Prior to the initial clinical implementation of per-oral endoscopic myotomy in October 2010, additional technical experience had been gained from a period of observation with H. Inoue at the Digestive Disease Center at the Showa University Northern Yokohama Hospital in Japan.

Stepwise technique for per-oral endoscopic myotomy

In the following, our surgical approach to flexible endoscopic submucosal myotomy is illustrated by the case of a 61-year-old male patient (BMI 21.41 kg/m^2) diagnosed with primary achalasia. The patient underwent several previous treatment attempts including one episode of Botulinum-Toxin injections as well as a pneumatic balloon dilatation of his LES. Preoperative esophageal manometry showed the patient to have an elevated LES resting pressure of 74 mmHg as well as an abnormal LES residual pressure of 18 mmHg. After informed consent the patient was enrolled in an ongoing clinical phase II study and was scheduled to have POEM. The study was approved by the Institutional Review Board at Providence Portland Medical Center Clinical, Trial number: NCT01302301, http://www.clinicaltrials.gov.

Under general anesthesia and in supine position, the patient was taken to the operative room and routine esophagogastroduodenoscopy (EGD) was performed using a high-resolution upper endoscope (GIF-H180J, Olympus, USA). Carbon dioxide (CO_2), instead of air, was used for insufflation. An esophageal overtube was placed and an angled dissection cap mounted onto the

tip of the endoscope to enable an effective submucosal view.

After the side of the lesser gastric curvature had been identified, three consecutive endolumenal injections of non-diluted methylene blue, beginning at the GEJ and marking every 2 cm at the patient's right-anterior side of the esophageal wall (1–2 o'clock position), were performed. These clearly blue-dyed submucosal markings facilitate later submucosal orientation during dissection within the esophageal wall.

Similar to the technique used for ESD, the esophageal mucosa was lifted from the muscular layer by injecting saline together with epinephrine and methylen blue, at the pre-defined location approximately 8 cm above the GEJ. Endoscopic needle-knife cautery was then used for the creation of a 1.5 cm longitudinal mucosotomy (Fig. 2). A 12 mm biliary extraction balloon is inserted into the submucosal space and is used to facilitate insertion of the flexible endoscope underneath the esophageal mucosa (Fig. 3).

The submucosal tunnel was created using the combination of blunt dissection, electro-cautery with a triangle tip needle-knife (TT-knife, Olympus, Tokyo, Japan) and the additional injection oft blue-dyed saline (Fig. 4). CO_2 insufflation via the endoscope also helps with the dissection. To ensure an adequate extension of the myotomy onto the stomach, the submucosal tunnel is extended far below the LES onto the gastric cardia.

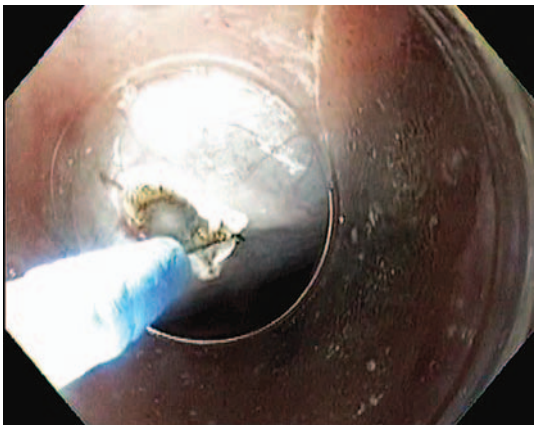

Fig. 2: The esophageal mucosotomy was created by needle-knife cautery after mucosal saline lift

Fig. 3: The biliary extraction balloon, inserted through the mucosotomy, was used to facilitate access into the esophageal submucosal space

Fig. 4: Dissection within the submucosal space above the GEJ using a triangle-tip needle-knife. Note the visible esophageal circular muscle fibers on the right and the mucosa on the left

After appropriate length of the submucosal tunnel has been endoscopically confirmed by a retroflexed view, the endoscope is re-inserted into the submucosal space. Using the triangle-tip needle knife, dissection of only the inner circular muscle layer and the sling fibers of the LES is performed starting approximately 4 cm above the LES and extending 2 to 3 cm below onto the gastric wall. Similar to the technique used with laparoscopic hook-knife cautery, the endoscopic needle knife is used for selectively lifting the circular muscle fibers and dividing them with monopolar coagulation current (Fig. 5). Care was taken to only divide the inner circular muscle layer, leaving the longitudinal muscle fibers intact.

As soon as the appropriate length of the partial myotomy was confirmed, smooth passage of the flexible endoscope through the GEJ was evaluated. The

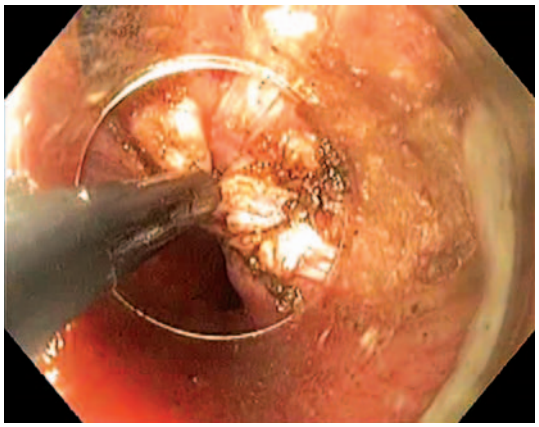

Fig. 5: The endoscopic triangle-tip needle-knife is also used for selectively dividing the circular muscle fibers, leaving the outer longitudinal fibers intact

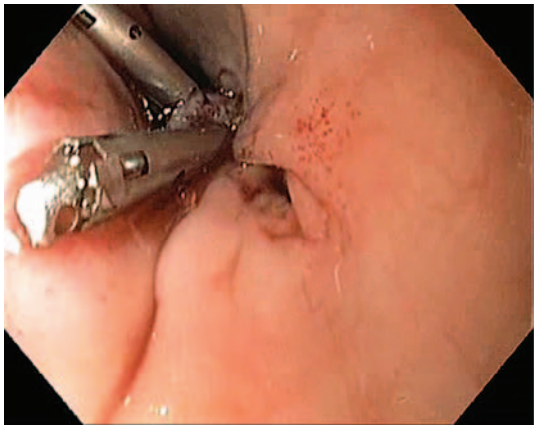

Fig. 6: The mucosotomy was closed using conventional endoscopic hemoclips (prior to the application of the last clip the residual mucosal opening can be seen)

esophageal mucosal incision was closed by an appropriate number of standard endoscopic hemoclips (Fig. 6).

The patient was scheduled for postoperative gastrografin esophagogram on the following morning and initial clinical follow-up at 2-weeks was planned.

Results

Preclinical observations

During our extensive preclinical work, the required steps for successful per-oral endoscopic esophageal myotomy have been defined. Typically, submucosal dissection in the animal models was found to be feasible by mainly blunt dissection until the GEJ was reached. When this anatomical landmark, where the mucosa was tighter attached to the muscular layer, was overcome by more tedious dissection, the submucosal space at the gastric cardia opened up easier again. In the porcine model it was also observed that, in contrast to the clinical setting, the substantially thinner esophageal muscle layers in the pig model, hampered precise division of solely the inner circular fibers. A partial myotomy was found to be only feasible right at the GEJ, but was barely possible proximal in the esophagus. Closure of the mucosotomy using standard endoscopic hemoclips was observed to be the most feasible in the animal models.

Clinical observations

With the patients under general anesthesia, the GEJ was located and the appropriate location for transmucosal access was easily defined during routine EGD. Measurements were repeated after the esophageal overtube had been placed including planed beginning and ending measurements for the myotomy. Subsequently, intramucosal blue-dye tattoos were placed as previously planned, along the right anterior (2 o'clock) position within the esophageal wall. A mucosal incision using an endoscopic needle knife cautery incision was performed after a saline "lift" at approximately 8 cm above the GEJ is made. With the aid of the biliary extraction balloon to accomplish the initial submucosal access, endoscope introduction into the submucosal space was easily accomplished and took 7 minutes from the time of the initial mucosal lifting.

A submucosal tunnel within the esophageal wall was carried out without any complications, using primarily the triangle-tip needle knife cautery, but also further saline injection, blunt dissection or hot biopsy forceps to coagulate larger submucosal vessels. At the LES, dissection was found to be more time-consuming due to the narrowness of the esophagus at that point. The end of the palisade vessels, which are also visible from the submucosal space, was additionally used as anatomical landmark to define the LES for further orientation. The completion of the "tunnel" in-between the mucosa and the muscle layers extending into the gastric cardia (11 cm length) took 32 minutes. Intermittent withdrawal of the endoscope and gastroscopy in retroflex view could confirm the appropriate orientation and length of the dissection onto the gastric cardia on the anterior side.

The partial myotomy, cutting only the clearly visible circular muscle fibers while leaving the longitudinal layer intact, was then precisely performed with the aid of the triangle-tip needle knife starting from 4 cm above the GEJ and extending the myotomy to 3 cm onto the gastric cardia. In this case the endoscopic myotomy itself took 124 minutes. The mucosotomy was closed with three standard endoscopic hemoclips, which took 6 minutes.

Intraoperatively, the blood pressure, heart rate, and ventilation parameters remained in the normal range for the duration of the procedure. On the next morning, no esophageal leakage was seen on the water-soluble esophagogram and the patient was discharged on postoperative day one. No perioperative complications were observed and at the two-week clinical follow-up the patient reported immediate symptom relief (dysphagia score = 0).

Discussion

Endoscopic treatments for achalasia have a long history. The most prominent procedure is fluoroscopic directed large diameter balloon dilation. While relatively effective it often requires multiple interventions and has a significant risk of esophageal perforation. In many areas laparoscopic myotomy has replaced balloon dilatation because of its precision, predictable outcomes, and ability to correct complications at the time they occur. A pure endoscopic technique for direct surgical division of the LES muscle using a needle-knife to cut the esophageal muscle from the lumenal side was reported [18] in 1980. However, the resulting unclosed breech of the mucosa and the circular muscle (leaving only the insubstantial longitudinal muscle layer) raised concerns about infectious complications or insufficient separation of the divided esophageal muscle edges and the procedure was never widely adopted. It took more than 25 years and the novel knowledge gained from experimental and clinical NOTES research [19], to reawake interest in the endoscopic surgical approach. Today, the feasibility and safety

of a translumenal access together with successful closure has been confirmed in several clinical studies [15]. Although potentially less familiar to surgeons, the submucosal space has also been discovered to be a novel and important area for surgical endoscopic procedures. Not only does the submucosal space provide a good dissection plane for endolumenal resection of early gastrointestinal malignancies using endoscopic submucosal dissection (ESD) techniques, but also provides space for either safe access from an endolumenal to an extralumenal cavity or even for the surgical intervention itself.

Although a flexible endoscopic submucosal myotomy challenges certain surgical dogmas, it has been observed to be safe and it provides a completely novel and very targeted approach to treat the symptoms of achalasia. The greatest appeal of the approach is that it specifically allows visualization and surgical division of only the inner circular esophageal muscle fibers, presumably the only affected LES component in achalasia. This has not been feasible with any other procedure so far. It is hypothesized that preserving the anatomical integrity of the lower esophageal sphincter anatomy, as POEM does, will minimize postoperative reflux and thereby the need for an added anti-reflux procedure with its inherent morbidity.

While promising, the long-term outcome of POEM remains unknown and even the longest practitioner [13] has yet to publish objective reflux testing after the surgery. Current proposals to treat whatever percentage of postoperative reflux there is, include the use of a subsequently performed endolumenal anti-reflux procedure as has been described in animal models [20]. This combined procedure would still avoid the more invasive surgical procedure of laparoscopic Heller myotomy with an anti-reflux procedure, which is the current gold standard. So far, the largest published clinical series documents only one of 17 patients complaining about mild reflux symptoms and having esophagitis of Los Angeles Grade B [13]. Concerns regarding the efficacy of only a partial circular muscle myotomy also need to be addressed. Theoretically this is the perfect operation for achalasia but whether it will last as long as a full myotomy will need to be answered.

Similar to the first clinical cases reported by the Japanese group, the myotomy in the case described was performed on the right/anterior esophageal side and extended onto the anterior lesser curvature of the stomach. A previous report on endoscopic submucosal myotomy theorized the potential benefit of a posterior approach [21]. The authors theorized that a later anterior surgical myotomy could still be performed if recurrent symptoms occurred. However, due to the preciseness of the endolumenal technique, an additional endoscopic myotomy on the opposite lumenal site might also be feasible, but this hypothesis has still to be evaluated.

During this experimental and clinical work, it has been observed that with a firm knowledge of endoscopic techniques and extensive preclinical training, this novel and potentially favorable endoscopic procedure can be safely introduced into a surgical practice. It also emphasizes that appropriate training opportunities as well as a certain expertise in flexible endoscopy will be necessary for the general surgical community. Technical refinements, such as blue-dye marking to facilitate submucosal orientation and use of a balloon to facilitate scope introduction, appeared to further enhance the safety and efficacy of this approach. Prospective data on long-term physiology are currently being collected at our institution.

The feasibility of endoscopic submucosal partial myotomy for achalasia is a perfect example of the true revolution caused by development efforts in NOTES. Although the long-term outcome and efficacy of POEM has still to be compared to already established procedures, the promise of this novel procedure seems more than obvious. Natural orifice surgery is not simply about reducing the invasiveness of already established procedures, but much more about the development of innovative surgical concepts and precise targeting of disease processes. Realizing this potential of NOTES developments beyond cholecystectomy, the current question regarding natural orifice surgery is not about what has been left from its hype, but rather what is still to come.

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Conflict of interest

Drs. Rieder, Dunst, Kastenmeier, Makris and Swanström have nothing to disclose.

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