**Name of Journal: *World Journal of Gastrointestinal Endoscopy***

**ESPS Manuscript NO: 20096**

**Manuscript Type: MINIREVIEWS**

**Peroral endoscopic myotomy: An emerging minimally invasive procedure for achalasia**

Vigneswaran Y *et al.* Novel endoscopic treatment for achalasia

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**Author contributions:** Vigneswaran Y contributed to the study idea, literature search, writing and final revision of the manuscript; Ujiki MB contributed to the writing and the final revision of the manuscript

**Conflict-of-interest** **statement:** Dr. Yalini Vigneswaran and Dr. Michael B Ujiki have no conflicts of interest that are related to the work submitted here for publication.

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**Received:** May 28, 2015

**Peer-review started:** May 31, 2015

**First decision:** August 18, 2015

**Revised:** August 25, 2015

**Accepted:** September 7, 2015

**Article in press:**

**Published online:**

**Abstract**

Peroral endoscopic myotomy (POEM) is an emerging minimally invasive procedure for the treatment of achalasia. Due to the improvements in endoscopic technology and techniques, this procedure allows for submucosal tunneling to safely endoscopically create a myotomy across the hypertensive lower esophageal sphincter. In the hands of skilled operators and experienced centers, the most common complications of this procedure are related to insufflation and accumulation of gas in the chest and abdominal cavities with relatively low risks of devastating complications such as perforation or delayed bleeding. Several centers worldwide have demonstrated the feasibility of this procedure in not only early achalasia but also other indications such as redo myotomy, sigmoid esophagus and spastic esophagus. Short-term outcomes have showed great clinical efficacy comparable to laparoscopic Heller myotomy (LHM). Concerns related to postoperative gastroesophageal reflux remain, however several groups have demonstrated comparable clinical and objective measures of reflux to LHM. Although long-term outcomes are necessary to better understand durability of the procedure, POEM appears to be a promising new procedure.

**Key words:** Endoscopy; Achalasia; Peroral endoscopic myotomy; Myotomy

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**Core tip:** With recent advancements in endoscopic techniques and technology, peroral endoscopic myotomy, also known as peroral endoscopic myotomy (POEM), has emerged as a promising minimally invasive procedure for treating achalasia. POEM uses the technique of endoscopic submucosal dissection to create a myotomy and palliate symptoms of achalasia. Although long-term outcomes are still needed, short-term outcomes show good safety and efficacy of the procedure that are comparable to laparoscopic Heller myotomy. In this review we will review the technical details of the procedure itself as well as the reported outcomes.

Vigneswaran Y, Ujiki MB. Peroral endoscopic myotomy: An emerging minimally invasive procedure for achalasia. *World J Gastrointest Endosc* 2015; In press

**INTRODUCTION**

Achalasia is a rare motility disorder of the esophagus that is characterized by non-relaxation of the lower esophageal sphincter and aperistalsis of the esophagus. No cure exists for this idiopathic disease and thus treatment is aimed at palliation of the esophagus to allow for adequate emptying of the esophagus and improvement of symptoms. Palliation requires disruption of the lower esophageal sphincter, which has been traditionally accomplished by botulinum toxin injection, balloon dilation or surgical myotomy. Endoscopic botulinum toxin treatment is not often the therapy of choice in these patients, due to the short-term therapeutic effect in this chronic disease. Pneumatic balloon dilation forcefully disrupts the sphincter fibers and although several groups have demonstrated efficacy with this technique, dilation is still associated with a significant risk of perforation[1]. Surgical myotomy has been conventionally performed laparoscopically by dividing the lower esophageal sphincter above and below, known as a laparoscopic Heller myotomy (LHM) and typically performed with concurrent anti-reflux procedure. Reports of long-term outcomes have shown the superior efficacy of LHM and thus are often the therapy of choice in many of these patients. However with the advances in technology and endoscopic techniques, this concept of a surgical myotomy has lead to the development of an endoscopic approach, peroral endoscopic myotomy (POEM).

**HISTORY AND DEVELOPMENT OF POEM**

The use of endoscopic treatment for achalasia was first reported in a case series in 1980 by Ortega *et al*[2] In this series of 17 patients, an endoscopic myotomy was performed using a modified needle knife to directly dissect through the mucosa into the muscular layer to perform a myotomy. Although showing good outcomes, at the time the technique was thought to be unsafe because a direct mucosal approach not only resulted in poor visualization of the muscular layer, but also could result in mediastinal contamination from luminal content. Additionally with limited available devices, the use of the needle knife did not allow for precise and controlled movement, which could potentially lead to high risks of perforation as well as injury to nearby structures. Although abandoned at that time, several decades later the evolution of natural orifice transluminal endoscopic surgery (NOTES) allowed for improvements in endoscopic techniques and technology that subsequently lead to the development of what we now know of as POEM.

As the growth of NOTES procedures continued, submucosal endoscopy developed as a method to not only work below the mucosa to remove mucosal disease, but also to safely enter sterile cavities by creating a mucosal flap to minimize contamination[3,4]. In 2007, Pasricha *et al*[5], using a pig model, reported the use of submucosal tunneling to create a mucosal flap and an esophageal myotomy which reduced LES pressure. This addressed the first problem of direct dissection through the mucosa and risk of mediastinal contamination, but the use of the balloon dilator has limitations, due to the inability to accurately position within the wall as well as the associated risks of injury. However in 2010, Inoue *et al*[6] reported a modified technique and presented the first case series of successfully performed POEM in humans. The two important alterations included: (1) the use of electrosurgery for the endoscopic submucosal dissection rather than a balloon dilator, which is described below; and (2) the use of a triangle-tip knife for muscle dissection, which allowed for precise dissection under direct visualization. Variations of this technique are now performed by specialized centers worldwide for the treatment of achalasia.

**OPERATIVE TECHNIQUE**

Under general anesthesia patients are positioned supine. POEM places these patients at high risk for subcutaneous emphysema and accumulation of gas in the body cavities thus CO2 should be used for insufflation and if possible positive pressure ventilation should be maintained at pressures higher than that of endoscopic insufflation to reduce the risk of these complications. Initial evaluation of the esophagus and stomach with a high-definition standard upper endoscope is performed to identify the gastroesophageal junction (GEJ). Once the GEJ is identified, an overtube is placed over the endoscope and dissecting cap placed on the endoscope. Approximately 10-15 cm proximal to the GEJ, the mucosa is injected with a mixture of methylene blue, saline, and epinephrine to create a mucosal bleb. Most groups perform this on the anterior aspect of the esophagus, however there may be variation to this positioning. If the patient is presenting for redo myotomy, the operator should typically perform the procedure on the right lateral aspect of the esophagus to avoid the previous myotomy site. The mucosotomy is then made to enter the submucosal space.

The submucosal tunnel is created from the mucosotomy along the lesser curvature to 2-3 cm distal to the GEJ where blanching is identified on the stomach side. The method to dissect this space is based on operator preference. The use of electrosurgery allows for a controlled dissection, with the use of either a triangular-tip knife (Olympus, Center Valey, PA, United States) or a T-type hybrid knife (ERBE, Tubingen, Germany). The alternative option is balloon dilation to develop the plane, however this is a less controlled method, as previously discussed.

The myotomy is started 2-3 cm distal to the mucosotomy and continued to the end of the tunnel at 2-3 cm distal to the GEJ. A partial myotomy is most commonly performed by careful dissection of the circular fibers only, avoiding the longitudinal fibers to avoid entry into the mediastinum. However several groups have explored the option of a complete myotomy through the longitudinal fibers as well[7,8]. The mucosotomy is then closed to avoid leak with the use of endoscopic clips or an endoscopic suturing device. After completion of the procedure, the scope should easily traverse the GEJ. The scope can be then removed and patient extubated and recovered.

**COMPLICATIONS AND ADVERSE EVENTS**

This invasive endoscopic procedure is not without risks and should only be performed at centers that are capable of treating these complications. Additionally POEM requires operators with specific surgical and endoscopic skills as well as a good understanding of esophageal motility disorders and the available interventions. All standard operative procedures should be followed, including appropriate preoperative evaluation and risk stratification of the patient. The most common complications encountered during or after POEM are listed in Table 1.

Inadvertent mucosotomy is a relatively common complication, especially early in the operators experience, due to the challenges in technique of submucosal tunneling. Although the clinical implications of mucosal injuries are unclear, most centers would recommend closing any defects prior to completion of the procedure to avoid any potential leaks. This is similar to full-thickness muscular injuries that in particular occur at the site of the initial mucosotomy.

Complications related to the insufflation are fairly common. These complications can be minimized by the use of CO2 rather than room air, due to the quick diffusion of CO2, and by also maintaining low insufflation pressures if possible. The subsequent complications due to insufflation are listed in Table 1 and in most cases have minimal clinical sequelae. However depending on the degree of gas accumulation in these cavities, the patient may require decompression as described in Table 1. All operators performing POEM should be aware of these risks and capable of treating them.

Similarly pleural effusions may commonly occur and depending on the degree of fluid accumulation and patient symptoms, may or may not require intervention. Delayed bleeding appears to be a rare complication of POEM (0.8%-2.7%)[9,10], but if diagnosed must be promptly intervened on. Lastly the most feared complication, esophageal leak with reported rates from 0 to 5.6%[7,11,12], can be a devastating complication if occurs. If the patient is slow to recover there should be high suspicion for gastrointestinal leak and appropriate work up with either endoscopy or imaging. The time to diagnosis of the leak in addition to the extent of the leak will largely determine the required interventions.

**SHORT TERM OUTCOMES**

Most centers perform this new procedure under institutional review board oversight as suggested by the NOSCAR POEM White Paper Committee[13] and thus several groups have published their initial outcomes. These preliminary results demonstrate highly skilled endoscopists can safely perform the procedure and short-term data suggests promising efficacy. Table 2 summarizes the reported outcomes seen by the experienced centers around the world.

Most centers evaluate efficacy based on symptomatic relief as measured by the Eckardt score and measure clinical success as Eckardt score ≤ 3. All of the centers described in Table 2 demonstrated significant improvement in Eckardt scores after POEM. At mean follow up from 1.5 to 12 mo, 89%-100% of patients received clinical success from POEM treatment[7,9-12,14,15]. Several centers also routinely use manometry postoperatively to evaluate the diagnostic outcomes after POEM, which revealed significant improvement in LES resting pressures[9,12,14]. When compared to patients undergoing a standard LHM, patients undergoing POEM had similar symptomatic relief and manometry findings[9,11,12,16]. Additionally quality of life improvements after POEM seem to be comparable to reported outcomes after LHM[17]. All of these results are promising, but only provide short-term results. Further observation is required to determine the durability of POEM outcomes at long-term follow up.

In addition to the durability, postoperative reflux after POEM has and continues to be a concern with the long-term outcomes. LHM, the gold standard for treatment of achalasia, has a reported occurrence of gastroesophageal reflux (GERD) anywhere from 20% to 100% after surgical myotomy without fundoplication[18,19]. This iatrogenic reflux due to the extensive disruption of the LES has lead to routine performance of an anti-reflux procedure in concurrence with the Heller myotomy. Thus without an anti-reflux procedure, GERD after POEM is an important endpoint for efficacy. Objective measures of GERD after POEM such as erosive esophagitis have been found at rates of 6%-40%[6,7,12,20] and abnormal pH studies at rates of 20%-40%[9,21]. Clinically, 4.9%-33%[6,7,12,20] of these patients have reflux symptoms and 4.9%-22% of patients appear to be restarted on proton pump inhibitor therapy after POEM[7,14,17]. However, all of these objective and clinical findings appear to be equivalent to LHM with fundoplication in several series[9,11,12,22]. The leading theory for possible comparable reflux outcomes is related to the maintained hiatal anatomy after POEM. With an endoscopic approach to the myotomy, the opportunity to preserve the longitudinal muscle fibers as well as not disrupting the GEJ innervation or the diaphragm and the phrenoesophageal ligament, may in fact be enough to avoid significantly worse GERD. However these reported outcomes of GERD are fairly short-term results and are difficult to compare to LHM outcomes because of the highly variable reported outcomes of reflux after LHM with fundoplication in the literature itself.

**SPECIAL PATIENT COHORTS**

Certain special patient cohorts have been studied as possible indications for POEM. These include patients with a previous failed Heller myotomy or POEM, sigmoid type achalasia, spastic esophagus and the pediatric patient. Due to the rarity of these cases, outcomes are not well understood but initial reports discussed below are encouraging.

***Redo myotomy***

Patents with failed LHM are difficult to treat. Traditionally patients who fail myotomy can be candidates for additional interventions including repeat Heller myotomy and as a last resort esophagectomy. However due to scarring and adhesive disease that develops around the GEJ from the initial operation, these redo cases can be quite challenging. Moreover, although repeat Heller myotomy is often successful, 20%-30% of patients will undergo this relatively risky procedure and still fail after second Heller myotomy[23,24]. Thus, POEM provides a unique opportunity to potentially treat these patients without enduring a challenging and involved operation. Several centers including our own have reported the use of POEM to treat patients with failed Heller myotomy. Initial outcomes show the procedure is safe and at short-term follow-up has 90%-100% success[25-27]. Even with previous fundoplication, the procedure is performed in these patients almost identical to patients without previous myotomy with exception of the location of the second myotomy. The recommendation is to avoid the previous myotomy that is conventionally performed anterior and to perform the repeat myotomy right lateral on the esophagus. Similar outcomes have been observed in those patients with previous POEM presenting for redo POEM[28].

***Sigmoid esophagus***

Sigmoid-shaped esophagus is often seen in advanced achalasia cases and can be a complicated disease to treat. Although initial approaches to treatment are debatable, most would advocate for treating these patients with myotomy before discussing esophagectomy[29-32]. The use of POEM in these advanced staged patients has been reported with good feasibility and short-term success[6,33]. However, due to the anatomical changes in the esophagus these cases are particularly challenging, especially when developing the submucosal space, and should only be performed by highly experienced operators.

***Spastic esophagus***

Spasitc disorders of the esophagus are characterized by abnormal contractility of the esophagus and can be divided into spastic achalasia, diffuse esophageal spasm (DES), and hypercontractile or jackhammer esophagus. These motility disorders are difficult to treat and often long-term clinical success is only accomplished with surgical myotomy[34]. Treating these patients with POEM is safe and at initial short term follow up is efficatious[35,36]. In a recent multicenter study which included 73 patients with spastic esophagus, when an extended myotomy was performed with POEM, 93% clinical success was observed at an average of 8 mo[37]. However as with POEM in the typical achalasia patient, longer term studies are necessary to understand the durability of these treatments.

***Pediatric patients***

Though rare, achalasia presenting in pediatrics patients can lead to significant problems with malnutrition and subsequently mental and physical development. These patients are not good candidates for endoscopic therapies due to short term durability with the growing child and the gold standard of treatment is surgical myotomy. Chen *et al*[38] demonstrated POEM can be safely performed for pediatric patients and in 27 patients showed 100% clinical success at an average of 25 mo and thus can be considered in a pediatric patient.

**CONCLUSION**

POEM is an emerging new technique for treating achalasia that evolved from the era of NOTES. POEM may also expand the therapeutic options for patients with challenging esophageal disease due to the growing indications, including patients with previous myotomy, sigmoid esophagus and spastic esophagus. Short-term results from experienced centers allow for cautious optimism with this minimally invasive technique, however questions remain as to long-term durability and subsequent GERD. Patients offered POEM should be counseled about our limited knowledge of long-term outcomes as well as the potential risk of GERD. Continued observation of long-term outcomes will be necessary as we continue to understand this procedure.

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**P-Reviewer:** Ramchandani M **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table 1 Complications after peroral endoscopic myotomy**

|  |  |
| --- | --- |
| Complication | Treatment |
| Mucosal injury | After completion of myotomy, mucosal defects should be closed to minimize risk of leak with clips or suturing device |
| Full thickness injury | Although certain centers have demonstrated safety with full thickness myotomy, if occurs at site of mucosotomy the operator must consider closure of this site to prevent potential leakage |
| Gas escape related complications | |
| Subcutaneous emphysema | Observation |
| Pneumomediastinum | Observation, unless physiologic symptoms |
| Pneumothorax | Small volume closely observed with oxygen only. Volume > 30% may require decompression |
| Pneumoperitoneum | Large volume or physiologic symptoms requires decompression of the abdomen with Veress needle insertion |
| Pleural effusion | Small volume can be observed and will absorb. Larger volumes with symptoms require drainage |
| Bleeding | Most common at the GEJ or distal on stomach side due to increased vascularity. Supportive care and transfusions, endoscopic re-exploration if warranted for hemostasis |
| Leak/Mediastinitis | Depending on time of presentation and extent of perforation will determine the interventions required, which may be as simple as endoscopic treatment or as severe as invasive surgical treatment |

GEJ: Gastroesophageal junction.

**Table 2 Reported outcomes for Large Volume Single Centers after peroral endoscopic myotomy**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Ref. | Study size | Myotomy thicknes/length | Morbidity | Follow up  (mo) | Clinical outcome - before/after | Manometrybefore/after | Postop PPI | |
| Inoue *et al*[14]  2013 | 300 | Partial  14.1 cm | Pneumothorax 0.3%  Mucosal Injury - 2.0% | 12 | Eckardt - 6.13/1.33  98.2% success | 27.3/13.4 | 4.9% |
| Ren *et al*[10]  2012 | 119 | Partial  9.2 cm | Pneumothorax - 25.2%  Pneumoperitoneum- 39.5%  Bleeding 0.8% | 3 | 98.3% success | NA | NA |
| Stavropoulos *et al*[15]  2013 | 45 | Full  9 cm | Mucosal Injury - 20%  Pneumoperitoneum- 13% | 2.5 | Eckardt - 7.8/0.4  95% success | NA | NA |
| Swanstrom *et al*[9]  2014 | 37 | Partial | Perforation - 10.8% Bleeding - 2.7% | 6.8 | Eckardt - 5.4/1.2  Dysphagia - 0% | 41/16 | NA |
| Ujiki *et al*[17]  2014 | 37 | Partial  12.8 cm | Perforation - 5.4%  Mucosal Injury - 2.7% | 11.3 | Eckardt - 6.8/0.6  100% success | 29.1/NA | 22% |
| Hungness *et al*[12]  2013 | 18 | Partial  9 cm | Perforation - 5.6% | 1.5 | Eckardt - 7/1  89% success | 19/9 | NA |
| von Renteln *et al*[7]  2012 | 16 | Partial and full  12 cm | Perforation - 0%  Pneumoperitoneum- 50% | 3 | Eckardt - 8.8/1.4  94% success | 27.2/11.8 | 6.3% |