Peroral endoscopic myotomy for achalasia—a review

Geoffrey Paul Kohn\textsuperscript{1,2}

\textsuperscript{1}Department of Surgery, Eastern Health Clinical School, Monash University, Melbourne, Australia; \textsuperscript{2}Melbourne Upper Gastrointestinal Surgical Group, Melbourne, Australia

Correspondence to: Geoffrey Paul Kohn. Suite 32, Cabrini Hospital Malvern, 181 Wattletree Rd, Malvern, Melbourne, Victoria 3144, Australia.
Email: gkohn@uppergi.net.

\textbf{Abstract:} Definitive treatment of achalasia usually involves disruption of the muscle fibers of the lower esophageal sphincter (LES). Over the past few decades the most common procedure to achieve this has been laparoscopic Heller myotomy (LHM) with partial fundoplication. Recently, peroral endoscopic myotomy (POEM) has been increasingly utilized. This manuscript reviews the current state of the POEM procedure in the treatment of achalasia. Safety and efficacy of the procedure have been demonstrated. Unanswered questions remain regarding the long-term incidence and implication of gastroesophageal reflux, as well as any possible benefits of the omission of an antireflux fundoplication when compared to Heller myotomy (HM).

\textbf{Keywords:} Achalasia; cardiomyotomy; natural orifice surgery; systematic review; esophageal motility disorders

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\textbf{Introduction}

Achalasia is a relatively rare cause of dysphagia manifest by esophageal aperistalsis and failure of relaxation of a hypertensive lower esophageal sphincter (LES). For many decades treatment has been directed towards facilitating reduction in sphincter pressure. While mechanical stretching methods with esophageal dilators and muscle relaxation with botulinum toxin injection have been commonly used as treatment modalities, the associated recidivism rates of the disease make them less than ideal options (1).

Guidelines suggest that the current gold standard treatment of achalasia is division of the LES mechanism (1). This myotomy aims to divide the circular muscle fibers of the LES while preserving the underlying esophageal mucosa intact. While initial approaches to myotomy were transthoracic, today a laparoscopic approach is far more common. To prevent gastroesophageal reflux after myotomy a concomitant fundoplication is recommended (1).

First reported by Inoue in 2010 (2), an endoscopic tunneled approach to myotomy, termed “peroral endoscopic myotomy” (POEM), is rapidly gaining popularity. The total number of POEM procedures performed worldwide is in the thousands, though exact numbers are difficult to determine as no centralized registry exists. The largest numbers are probably from Asia, with more than 1,300 having been performed in China (3) and more than 1,000 in Japan (4).

Proposed benefits of this approach include the ability to perform a longer myotomy, less disruption of the angle of His anatomy that may obviate the need for a concomitant fundoplication, a less morbid procedure, a better cosmetic result, and possibly a quicker recovery. In addition, POEM has been performed in patients with recurrent dysphagia after prior surgical myotomy where the ability to perform the endoscopic procedure through virginal tissue planes is beneficial.

\textbf{Indications for POEM}

Most initial reports of POEM were for the indication of symptomatic achalasia with progressive dysphagia or weight loss. The vast majority of these were for POEM as a primary therapy of achalasia and this indication forms the focus of
this manuscript. However, with increasing experience the indications have broadened (5). POEM has been applied as a revisional procedure after prior medical therapy, dilatation (6), or surgical myotomy (7,8). By permitting myotomy on any aspect of the esophagus and particularly posteriorly, POEM allows a virginal tissue plane to be developed away from a previous myotomy (9).

As compared to transabdominal or transthoracic myotomy, the myotomy performed during POEM is easier to extend into both the chest and the abdomen, allowing for a longer myotomy. This feature has made POEM an option for the treatment of distal esophageal spasm (10-12) and esophageal hypercontractility (“Jackhammer esophagus”, including hypertensive “nutcracker esophagus”) (13-16). Resolution of chest pain associated with jackhammer esophagus or distal esophageal spasm has been reported in case studies to occur in over 90% of patients (17). The indications for the natural orifice endoluminal approach of POEM has been expanded to the treatment of gastroparesis with an endoscopic tunneled pyloromyotomy, so-called G-POEM (18).

**Patient preparation for the procedure**

The diagnosis of achalasia or other indication must be confirmed with esophageal manometry, and other investigations as required. According to surveys of experienced POEM practitioners, certain comorbidities should be considered as contraindications for POEM, including prior mediastinal irradiation, severe pulmonary disease, coagulopathy, or portal hypertension even without evidence of esophageal varices (5). Some physicians prescribe antibiotics or antifungal medications preoperatively (19). The procedure is performed under general anesthesia with endotracheal intubation. This protects the airway and allows positive pressure ventilation, which reduces the risk and extent of mediastinal emphysema. The upper abdomen may be prepared with antiseptic to allow access for needle decompression to prevent significant abdominal distention during the procedure that might lead to abdominal compartment syndrome.

**POEM technique**

Inoue initially described an 8 cm myotomy (2 cm below the gastroesophageal junction and 6 cm above), though this has been extended to greater than 12 cm in some studies (19) and also reduced in others (20). At the commencement of the procedure, endoscopic evaluation of the esophagus and the stomach is performed and the landmarks of the LES and of the planned location of mucosotomy are identified. Carbon dioxide insufflation is used; air insufflation is contraindicated (20,21) due to a higher risk of complications such as pneumothorax. A high-definition forward-viewing gastroscope with a plastic cap is used (5). The esophageal mucosa is breached more proximally via a longitudinal mucosotomy to allow introduction of the endoscope into the submucosal space (Figure 1). Whether the mucosotomy is made in the anterior or the posterior aspect of the esophagus is at the discretion of the physician (5,22), though performance of the procedure through virginal tissue planes seems reasonable; after failed anterior Heller myotomy (HM), a posterior esophageal POEM is effective (3,23). The submucosal tunnel (Figure 2) is extended beyond the LES onto the gastric wall. This is confirmed by retroflex view in the stomach confirming submucosal staining of the gastric mucosa with injectate. Various solutions have been used
for the injectate, including indigo carmine, methylene blue and patent blue V. The circular esophageal muscle layer is then divided by electrocautery under vision starting either proximally or distally (Figure 3). Though the longitudinal esophageal muscle layer does not require division, if divided there appears to be no adverse effect on outcome (24). The proximal extent of the myotomy should be 2 cm distal to the distal point of the mucosotomy to allow a flap closure of the mucosa and presumed decrease in postoperative esophageal leak. After the myotomy is completed, the mucosotomy is closed using either endoscopic clips or suturing devices (Figure 4). Some physicians irrigate the submucosal tunnel with saline or antibiotic solution prior to closure.

A postprocedure gastroscopy is performed to confirm mucosal integrity. Postoperative contrast radiology, either a contrast esophagram or a CT (25), is often performed to confirm passage of contrast through the gastroesophageal junction without extravasation. These tests are very sensitive in detecting radiological leaks but the rate of clinically significant leaks is lower and investigation may not always be required (26).

**Outcomes**

Systematic review of the POEM literature is limited by marked heterogeneity of patient populations, techniques, reported outcomes and timepoints, making evaluation of effects difficult. Rather than making firm conclusions, a narrative description of comparative effects is all that may be usefully produced.

**Safety of the procedure**

The safety of POEM is well established and perioperative morbidity is comparable to that seen after LHM. The existing literature demonstrates a low incidence of complications after POEM in both adults and children (19,27-38). A pooled analysis found a 0.3% incidence of leak after POEM (39); early in one particular series the leak rate was 6% (17) suggesting a learning curve effect. The overall serious adverse event rate in one of the largest single center series (n=500) was 3.2%; all were managed conservatively with no perioperative mortality (40,41). Mucosal perforation rates vary between 0 and 25% is reported series, but are usually less than 10% (40). Comparative studies show near equivalence or perforation rates between POEM and LHM (42-49). The vast majority can be repaired endoscopically (50), and the effect of these perforations is usually minimal.

Rates of complications including leak are comparable to LHM (38,51) and surrogate measures of these leaks, such as unexpected Intensive Care Unit admissions, show no difference in comparative studies (43,45,48,49). Reported POEM-related complications include the development of subcutaneous emphysema, mediastinal emphysema, mediastinitis, pleural effusion, pneumothorax, pneumoperitoneum, peritonitis, delayed hemorrhage, and atrial fibrillation (21,52-54). While the majority of these complications can also occur after a surgical myotomy, complications unique to POEM such as retention of the endoscopic submucosal dissection cap, gas-related complications and dehiscence of the mucosotomy closure leading to food retention have also been reported (52,55-57).

Bleeding can occur during the POEM procedure or postoperatively into the submucosal tunnel. This can be severe, causing hematemesis, retrosternal pain or hemorrhagic shock (40). The incidence of severe bleeding is approximately 1.1% in a large metanalysis (39).
Delayed postoperative bleeding occurs in less than 1% of procedures (32,41,58). Procedure-related deaths are very rare and similar to rates after LHM (45).

Based on non-randomized cohort studies, it appears that POEM has a shorter operating time with less perioperative blood loss than LHM (38,43,47,59-64).

In regards to requirements for postoperative analgesia, one study reported similar postoperative pain scores and analgesic requirements between POEM and LHM (35,43), while others found patients had less pain after POEM (47). A systematic review of the available evidence has not demonstrated a significant difference in postoperative pain scores (65). Hospital length of stay and time to return to normal diet are similar between POEM and LHM (59,65).

**Dysphagia**

As a key outcome measure, the resolution of dysphagia after POEM is achieved in up to 95% (32,56) of patients in the short-term. POEM has been demonstrated to consistently reduce LES pressure (28,66), increase gastroesophageal junction diameter (67), and promote esophageal emptying (68,69). Long-term relief of dysphagia is lower (70) and has been reported to be 80% at 2 years (71).

Early dysphagia after POEM has been shown to be lower compared to LHM, possibly due to the lesser manipulation and subsequent inflammation and edema at the gastroesophageal junction after POEM (38). On the other hand, noncomparative studies have suggested Eckhart dysphagia scores to be equivalent between the two procedures at 6 months, with both procedures improving dysphagia in more than 95% of patients. This is likely a direct result of similar decreases in lower esophageal sphincter pressure observed after both procedures. One study reported that postmyotomy LES resting pressures but not LES relaxation pressures were higher after POEM than after LHM (38), without effect on dysphagia rates.

Comparative studies strongly support equivalence in improvement of dysphagia symptoms for POEM and LHM (38,44,49,59,64,72) with this finding supported by other systematic reviews (35,65), though with a possible greater efficacy of POEM at least in the short-term (59,60,73,74). Also, there are equivalent improvements in the integrated relaxation pressure of the lower esophageal sphincter (61,66).

Few comparative studies have examined Eckhardt dysphagia scores for POEM vs. HM (48,64), but results seem similar with equivalent Eckhardt scores are seen at 1 year post-procedure.

There is also some evidence supporting the benefit of POEM over pneumatic dilatation in the improvement of dysphagia (75,76).

Much has been written about the presumed benefit of POEM over HM in the treatment of achalasia subtype III due to the fact that it is easier to extend the myotomy proximally in the endoscopic procedure. However, there is a marked paucity of data to support a recommendation in this respect, and some data to the contrary (77).

With both efficacy and safety having been demonstrated as equivalent, the major outcomes of interest in deciding upon POEM versus LHM for the treatment of achalasia are long-term rates of gastro-esophageal reflux (GER) and long-term quality of life (QOL) scores. Additionally, as most HM operations are accompanied by a partial fundoplication, a comparison of fundoplication-related side-effects must be considered, including bloating, rectal flatulence and the ability to belch. These outcomes have been evaluated to varying degrees in the body of literature currently available.

**Gastroesophageal reflux**

Fundoplication is strongly recommended to be performed at the time of LHM (78,79), as without it many patients will develop evidence of reflux. It has been argued that the lack of mobilization of the esophagus at the diaphragmatic hiatus during POEM may decrease postoperative reflux and therefore make a fundoplication unnecessary after this procedure, and prevent potential fundoplication associated functional side-effects such as gas bloat. Nevertheless, GER is common after POEM and studies have documented abnormal distal esophageal acid exposure in one-third to one-half of patients following POEM (17,32,38,80).

Gastroesophageal reflux results from increased distensibility of the lower esophageal sphincter zone and it has been postulated—as POEM results in higher distensibility index of this area as compared to HM with fundoplication (74)—that POEM may result in higher rates of GER. However, evidence for this is lacking and a major limitation of the literature is a marked absence of prospectively collected comparative postoperative pH data for POEM and other procedures. It is possible that the postoperative distensibility index, as measured by EndoFLIP (EndoFLIP, Medtronic, USA), may be more of a predictor for long-term GER rather than the procedure itself (74,81).

Systematic reviews have concluded that both short-
and long-term GER symptoms (as opposed to objective evidence for reflux) are comparable between POEM and HM (73), based on some comparative data (38). There is a poor correlation between elevated distal esophageal acid exposure post-POEM and symptoms of reflux (82). Indeed, in patient populations reviewed after previous antireflux surgery, the use of PPI medications was actually poorly correlated associated with objective evidence of recurrent and it seems reasonable to expect the situation to not be dissimilar post POEM procedure (82).

Some noncomparative studies have reported heartburn or esophagitis in approximately 25% of patients after POEM (32) but severe esophagitis and reflux strictures have also been reported (71). Strictures can result in late recurrence of dysphagia and have led some to recommend routine post-POEM use of proton pump inhibitor medication (71).

There is little in the way of comparative data of GER rates between POEM and HM. That which exists supports near equivalence of GER, at least in the short-term (38,45,49,83), though with a probable trend towards higher long-term rates post POEM (61,84).

**Quality of life**

Disease-specific and general QOL scores have both been reported to improve after POEM, with improvements in SF-36 scores, emotional wellbeing, social functioning and general health evident at 6 months after the procedure (33,47,85). Comparison with HM shows similar improvements in postoperative global quality of life scores (63).

**Post-fundoplication symptoms**

No comparative studies exist comparing bloating after HM and POEM. Further investigation with longer term GER outcomes after POEM is needed. This area of study is particularly important as the putative cause of bloating—the fundoplication—is routinely performed after HM but not after POEM or pneumatic dilatation (withstanding the availability of some techniques of endoscopic fundoplication).

**Learning curve**

POEM requires a demanding skill set that involves both advanced endoscopic skills and knowledge of surgical anatomy and complication management.

Proctoring is necessary for the first few cases to ensure good outcomes. The number of proctored cases should be based on the endoscopic skills of the surgeon and how quickly they learn the technique (3,86,87). Improvements in operating time and ease of performing the procedure have been reported to occur between 20 and 60 cases (88-91).

**Cost**

Very little comparative data exists between POEM and alternative procedures. One identified study suggested a cost-saving of great than USD $3,000 ($17,782 vs. $14,481) for the POEM procedure over robotic HM (62) when performed in a major United States medical center. Others, also based in the United States have found similarities in cost between standard HM and POEM (92), perhaps favoring POEM in the long-term but with a large degree of uncertainty in the actuarial analysis (93).

**Direction for further study**

Some major questions still exist regarding comparative outcomes between POEM, LHM and esophageal pneumatic dilatation:

- Which procedure has the lowest rate of long-term GERD as determined by objective criteria of positive pH studies or reflux esophagitis?
- Does the absence of a fundoplication with the POEM procedure improve the incidence of postoperative bloating and improve quality of life as compared to HM?

These questions will only be answered by further comparative studies. Encouragingly, randomized controlled trials are currently ongoing comparing POEM with LHM (NCT01601678) and POEM vs. pneumatic dilation (NCT01793922) and are expected to report their results within the next few years.

**Summary**

With large number of POEM procedures now having been performed world-wide, the procedure has been demonstrated to be safe and effective in the management of achalasia. The procedure has certainly moved beyond the experimental phase into an era of ongoing outcomes surveillance. Furthermore, POEM has shown utility for use in revisional surgery.

Questions remain about the objectively-diagnosed
incidence and implications of GER after the POEM procedure. Questions also remain regarding the prevalence and effect of postoperative bloating, rectal flatulence and inability to belch in POEM as compared to LHM with fundoplication. These two areas should be the focus of future comparative trials.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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