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Review Article

Gastroesophageal reflux disease after peroral endoscopic myotomy: Facts and fictions

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A B S T R A C T

Peroral endoscopic myotomy (POEM) has today evolved to be the gold standard for the treatment of achalasia cardia and other spastic esophageal disorders. Its minimal invasive nature, safety and encouraging outcomes have made POEM the most commonly practiced submucosal tunneling procedure. Gastroesophageal reflux disease (GERD) or abnormal esophageal acid exposure time (AET), however, continues to haunt and dampen the encouraging clinical outcome after a POEM procedure. This is mainly because as against a laparoscopic Heller's myotomy, the procedure of POEM is not combined with an anti-reflux procedure. The incidence of GERD or AET after the POEM procedure has been shown to be, however, dissimilar in various studies. This is probably due to the inconsistency in the definitions of GERD and AET seen on 24-hr-pH studies. It is a known fact that continued abnormal esophageal acid exposure can lead to erosive esophagitis, Barrett's metaplasia, and esophageal cancer in the long run. Current literature also suggests that almost 50% of patients do develop abnormal acid exposure after a POEM procedure though only around one third develop symptoms or have erosive esophagitis. This concern has led to the development of techniques like POEM with fundoplication wherein an endoscopic fundoplication is performed in the same sitting of the POEM procedure, or even some techniques of endoscopic full-thickness plication/trans-oral incisionless fundoplication which can be performed after the POEM procedure selectively. Given the fact that almost 50% of patients undergoing POEM do develop an abnormal acid exposure, it is imperative that we need to clearly develop a rational strategy to deal with this reality. This review aims to realign the facts and fictions of the menace of post-POEM GERD and suggest a rational algorithmic approach.

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Keywords: Achalasia; Gastroesophageal reflux; Peroral endoscopic myotomy; Risk factors

Introduction

Peroral endoscopic myotomy (POEM) has been on the horizon for over a decade and has evolved to be the gold standard for the treatment of achalasia cardia and other spastic disorders of the esophagus.^{1–3} Its minimally invasive nature, safety and good clinical outcomes have contributed to the success of the POEM procedure.⁴ However, the fact remains that as compared to laparoscopic Heller's myotomy (LHM), POEM is not combined with a fundoplication procedure. This potentially increases the risk of abnormal esophageal acid exposure post POEM and its deleterious effects.⁵

Though majority of the patients after POEM are asymptomatic, pH studies have revealed that abnormal esophageal acid exposure time (AET) can occur in almost 50% of the patients after the POEM procedure.^{5,6} Keeping this in mind, Inoue et al⁷ described the technique of POEM with fundoplication (POEM-F) wherein an endoscopic fundoplication procedure is added during the primary

POEM procedure itself akin to the surgical technique. Our review highlights the facts and fictions of gastroesophageal reflux disease (GERD)/AET after the POEM procedure and proposes a rational algorithm of management of this burning issue.

GERD Post-POEM: Evaporating the Disillusion

It is important to understand that the definitions, interpretation and reporting of post-POEM GERD are still evolving and still there is no consensus. Due to the lack of standardized definitions, there is wide variation in reporting the incidence of GERD after POEM with some studies having reported an alarming 40% to 60% incidence of post-POEM abnormal AET on 24-hr-pH studies and endoscopic evidence of erosive esophagitis in 18%–40% with only 5% having severe grade C/D esophagitis.^{8–11} One needs to understand that this reported post-POEM abnormal AET could be, due to true GERD or secondary to fermentation related to food

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stasis which may exist before performing POEM.^{12,13} On manual review of 24-hr-pH metry findings majority of the time abnormal AET is due to fermentation rather than GERD. Such elevated AET can be of two varieties. i) sharp drop in pH < 3 and slow clearance, typical of true GERD or (ii) slow drop in pH rarely dropping below pH 3.7, which is typical of fermentation.^{14,15} If 24-hr-pH studies are not manually reviewed one may oversee these crucial factors while defining AET. Additionally, the cut-offs for AET have varied from 4%–5% for a pH < 4, with a DeMeester score > 14.72. Recently, in 2018 the Lyon Consensus for the diagnosis of GERD was published.¹⁶ However, post-POEM patients have been omitted in this consensus. Patients who have an AET > 6%, Los Angeles classification (LA) grade C/D esophagitis, long segment Barrett's or peptic stricture were considered to have a strong evidence for GERD. Whereas AET < 4%, normal endoscopy appearance was against GERD and AET 4%–6%, LA grade A/B esophagitis was considered inconclusive. It is worth bearing in mind that these three key points in the consensus do not take into consideration the patients symptom association. A pH < 3 with an AET of < 2.9% should ideally be used as the standard in achalasia patients. It would be ideal if we use the Lyon Consensus and combine it with patients' symptom association as well as the reflux episodes in post-POEM patients. Up to 30% of patients with typical reflux symptoms can have an absolutely normal pH study.¹⁷ The reference ranges are not validated in post-POEM patients. Patients with abnormal AET need not to have esophagitis or reflux symptoms, whereas, patients with esophagitis on endoscopy or abnormal pH studies can be asymptomatic. In a recent systematic review and meta-analysis with 17 studies and 1,542 patients the rate of abnormal 24-hr-pH testing and esophagitis occurred in 39% and 29.4%, respectively.¹⁸

It is also important to note that many patients who undergo the POEM procedure are found to have mucosal edema or mucosal injury which may interfere with results of 24-hr-pH metry. As these changes usually resolve within a month, 24-hr-pH metry done 1 month after the POEM procedure looks appropriate. There have been studies which have done 24-hr-pH metry at 1-, 2-,

and 3-month, but these have a research perspective. Performing a 24-hr-pH metry in the early course of recovery after the POEM procedure can lead to falsified results. Some common facts and fictions have been highlighted in Table 1.

Fundamental Difference between the POEM Procedure and LHM and Its Relation to Post Procedure GERD

In an interesting publication by Pandolfino et al¹⁹ in 2007, the esophago-gastric junction mechanism was spatially studied by high resolution manometry. In this study, the role of the inspiratory crural mechanism of the diaphragm and the expiratory lower esophageal sphincter (LES) muscle was studied in relation to their role in the normal anti-reflux mechanism. The study interestingly concluded that the reduced inspiratory crural diaphragmatic function was the only independent predictor of GERD. During a LHM, this inspiratory diaphragmatic crural mechanism is disturbed due to the hiatal dissection and incision of the phrenoesophageal ligaments. This is the reason that every LHM procedure is combined with an anti-reflux procedure. However, during the POEM procedure, only the LES muscle fibres are cut, keeping the diaphragmatic crural function intact. Therefore, those patients having a normal crural function are unlikely to develop significant GERD after the POEM procedure.

Technique of POEM and Its Relation to GERD (Anterior vs Posterior)

During the POEM procedure with an anterior approach, the sling fibres of the stomach are spared. This potentially reduces the chances of post procedure GERD. However, there is a risk of cutting these sling fibres if the traditional posterior approach is used (Fig. 1). In a single centred retrospective study, a trend towards increased abnormal AET was seen with the posterior POEM (posterior 50% vs anterior 36%) though insignificant.²⁰ This was just published as an abstract and the original study was never reported. In a subsequent study there was no difference in the rate of macroscopic esophagitis but there was a significant difference in abnormal DeMeester score (posterior 37% vs anterior 16%, $P=0.04$).²¹ The sling fibres can be however spared and inci-

Table 1 Facts and Fictions in Development of GERD after POEM

Fiction	Fact
GERD after POEM is very common	Abnormal acid exposure post-POEM is common, however, warrants redefining AET
GERD is seen in all patients after POEM	Seen in only about 50% of patients
All patients need to be treated with antireflux procedure	About 50% patients with GERD post-POEM have abnormal acid exposure, but are asymptomatic, hence, don't need intervention. Only 10% of symptomatic patients might need future intervention
Reflux will kill POEM	POEM has established itself, hence, about to stay for a long period of time in spite of reflux
POEM-F is the standard of care	Surgical fundoplication also doesn't stay for a long period of time and there is recurrence of symptoms. POEM-F has problems
High acid exposure time post POEM corresponds to GERD	Post-POEM, about 50% of patients with abnormal AET might be attributed to fermentation. Lyon Consensus, patient symptoms and frequency need to be considered
POEM results in postoperative reflux and fundoplication is necessary in all	Postoperative reflux is asymptomatic in majority of the cases and fundoplication is necessary in symptomatic patients with abnormal 24-hr-pH metry findings

GERD, gastroesophageal reflux disease; POEM, peroral endoscopic myotomy; AET, acid exposure time; POEM-F, POEM with fundoplication.

Fig. 1. Anatomy of lower esophagus and muscle fibers surrounding lower esophageal sphincter and stomach.

dence of GERD reduced by modifying the technique of posterior POEM as demonstrated by Shiwaku et al.²²

Depth and Length of Myotomy and Its Relation to GERD

In the traditional technique of POEM only a circular myotomy is performed (Fig. 2). However, many endoscopists perform a full-thickness myotomy as it reduces the procedure time and can be performed safely. Some studies have shown that full-thickness myotomy can be associated with higher chance of developing postoperative GERD.²³ However, there have been no randomized studies in this regard. In a retrospective study of 234 post-POEM patients there was no difference found in macroscopic esophagitis (full-thickness 21.2% vs selective 16.5%, $P = 0.38$).²⁴ Similar results were seen in another retrospective study published in 2017.²⁵ In a Chinese study by Wang et al,²⁶ clinically relevant GERD defined as abnormal AET with reflux symptoms and/or esophagitis was significantly higher with full-thickness myotomy (full-thickness 37.5% vs selective 12.5%, $P=0.028$). This could imply that full-thickness myotomy may increase the risk of post-POEM GERD. However, based on the limited retrospective series, there does not appear to be a definitive evidence to suggest that a full-thickness myotomy significantly increases the incidence of post POEM GERD. The choice therefore of choosing a partial or full-thickness myotomy rests on the comfort level of the endoscopist.

Surgical literature has suggested that performing a long (> 1 cm) gastric myotomy increases the risk of GERD.^{27,28} However, during a POEM procedure, a 2–3 cm gastric myotomy has been shown to be more efficacious as compared to < 2 cm myotomy.²⁷ The im-

portant technical issue which is followed by most POEM experts is to continue the gastric myotomy to the right of the perforating vessels seen while crossing the gastroesophageal junction. The double scope technique is useful to determine if the gastric myotomy has been adequate in length.

GERD after POEM: Whom to Treat and Whom to Manage Conservatively?

Severity index of GERD needs to be considered to initiate treatment. The frequency of symptoms along with 24-hr-pH studies is ideal for aiding decision making. In symptomatic patients with abnormal acid exposure, proton pump inhibitors (PPI) on demand have shown to give good symptomatic relief. Some patients might need lifelong acid suppression therapy. Additional endoscopic anti-reflux procedures should be reserved for those with worsening symptoms and dependent on PPI and who have an endoscopic evidence of severe reflux grade C/D esophagitis.²⁹ Asymptomatic patients should be advised to undergo routine surveillance and lifelong screening. All patients need to undergo routine endoscopic surveillance (once in 2 years) and a 24-hr-pH metry as appropriate.

Endoscopic full-thickness plication or transoral incisionless fundoplication procedure has been described after the POEM procedure in a case report and small case series to address the problem of post-POEM GERD.³⁰ In a study of 5 patients, endoscopic trans-oral incisionless fundoplication was described using the Esophyx2 device (EndoGastric Solutions, Redmond, WA, USA). The procedure was successfully performed in all patients with resolution of esophagitis and discontinuation of PPI in all four.³⁰

Fig. 2. Simplified steps in performing peroral endoscopic myotomy. Mucosal incision is done in mid esophagus after saline indigo carmine instillation into the submucosa. Submucosal tunneling (precedes muscle cutting) till gastroesophageal junction. Muscle cutting at 4 cm below the mucosal incision, mucosal incision is closed with standard endoscopic hemoclips. (A) Indigo carmine instillation into the submucosa. (B) Mucosal incision. (C) Submucosal tunneling till gastroesophageal junction. (D, E) Muscle cutting at 4 cm below the mucosal incision. (F) Mucosal incision closed with endoscopic hemoclips.

Such endoscopic fundoplication is performed in patients without achalasia with good results and the ability of such endoscopic fundoplication to alleviate symptoms due to GERD after POEM should be considered.

Is POEM-F the Answer to Post-POEM GERD? Is It Here to Stay?

Recently Inoue et al⁷ described a novel procedure combining POEM-F in the same sitting to reduce post-POEM GERD. POEM-F is a true example of NOTES (natural orifice transoral endoscopic surgery). Here, during an anterior POEM, an endoscopic fundoplication is performed after going out of the lumen into the abdominal cavity just below the diaphragmatic crus. This procedure is performed by going across the sub-diaphragmatic fat pad and the visceral peritoneum into the abdominal cavity. Then after locating the gastric fundus, it is grasped and pulled as well as attached to the muscle layer in the tunnel using a loop and clipping technique. The entire procedure is monitored and controlled by a dual endoscope technique using an ultrathin endoscope along with a normal upper gastrointestinal scope. After its description,

the POEM-F procedure attracted a lot of attention as it was attempting to be comparable to the LHM along with fundoplication. However, as this procedure entails an entry into the peritoneal cavity, it does mandate the endoscopist to understand the intra-peritoneal anatomy. In addition, this procedure though appears to be promising can be technically challenging and potentially be associated with adverse events. In spite of the initial enthusiasm, this procedure is still not practiced routinely because of its potential technical difficulties and adverse events. The main difficulty is to locate the exact exit point below the LES into the peritoneal cavity. The second is the potential fear of inadvertently entering the chest instead of the peritoneum causing a pneumothorax. The other issues which would need to be addressed are the fate of the endoclips which are likely to erode through the tunnel and finally the durability of the fundal wrap. Inoue et al⁷ described this procedure in 21 patients and found the fundal wrap to be well maintained at 1 month of the procedure in 95% of the patients. Long-term assessment of patients undergoing this procedure, however, still needs to be studied. We know even a surgical fundoplication remains intact in only 1/3rd of the patients in the long-term. Therefore, it is imperative that the fate of a POEM-F using clips

Fig. 3. Algorithmic approach for patients undergoing peroral endoscopic myotomy (POEM) and subsequent management of gastroesophageal reflux disease (GERD). PPI, proton pump inhibitor; EGD, esophagogastroduodenoscopy; LA, Los Angeles classification.

and loops require to be carefully studied in long-term studies. Patients undergoing this procedure may have an initial impact on the esophageal acid exposure but long-term results need to be carefully studied and monitored. It has been studied and proven that only around 50% of patients develop abnormal acid exposure after a POEM procedure and out of these only around 10% are symptomatic. Therefore, it seems to be unwise to perform a procedure of POEM-F in all the patients. We still do not have any specific criteria which can predict post-POEM GERD. Therefore, until this is possible, it would not be prudent to perform a POEM-F procedure in all the patients. This would make this procedure unindicated in 50% who are not likely to develop GERD. Therefore, currently, GERD after POEM is a reality which needs careful identification and management. PPI should be considered as first line of therapy and response to PPI should be carefully monitored. POEM technique should be modified to reduce post procedure GERD. An additional endoscopic anti-reflux procedure should be considered only for those patients who have significant GERD symptoms and those patients who are dependent on PPI's. Currently, there is insufficient data to recommend partial or total fundoplication in these patients. We suggest to use an algorithm for management of these cases (Fig. 3).

Conclusions

POEM is a safe, effective procedure for achalasia cardia with promising results in the medium- and long-term. Patients undergoing POEM need to be counselled regarding the possibility of developing GERD. The pre-POEM consent needs to be modified to include GERD as future complication of POEM. Post-POEM patients should be advised to undergo 24-hr-pH metry as appropriate and standardized guidelines need to be made to identify true GERD and fermentation. All patients post-POEM need to undergo routine endoscopic surveillance (once in 2 years). Certainly, there is no reliable endoscopic anti-reflux procedure in these patients, hence, antireflux procedures need to be evaluated only in symptomatic patients who fail optimal therapy and lifestyle modifications. There are various myths with regard to GERD post-POEM, however, with more prospective studies focusing on GERD, we can have more facts about this issue, we realize that more than facts, we have a lot of fiction which needs to be carefully evaluated. Currently, we are still in the search for a successful long-term rational approach to the holy grail of GERD after the POEM procedure.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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