

Peroral endoscopic myotomy: Time to change our opinion regarding the treatment of achalasia?

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Author contributions: Both authors contributed to the literature review and the writing of the paper; Tantau M reviewed the paper and made the final corrections.

Conflict-of-interest: None.

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Received: August 29, 2014

Peer-review started: August 30, 2014

First decision: November 1, 2014

Revised: November 15, 2014

Accepted: December 16, 2014

Article in press: December 17, 2014

Published online: March 16, 2015

90% of treated patients, with encouraging manometric outcomes and low incidence of postprocedural gastroesophageal reflux. The effectiveness of this novel therapy requires long-term follow-up and comparative studies with other treatment modalities for achalasia. This technique requires experts in interventional endoscopy, with a learning curve requiring more than 20 cases, including training on animal and cadaver models, and with a need for structured proctoring during the first cases. This review aims to summarize the data on the technique, outcomes, safety and learning curve of this new endoscopic treatment of achalasia.

Key words: Peroral endoscopic myotomy; Achalasia; Myotomy; Endoscopic treatment

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Core tip: This review aims to highlight the importance of a new minimally invasive technique for the treatment of achalasia, compared to classical surgical treatment. Although discovered recently, this method has already imposed itself as a safe and very efficient therapy. The difficult issue in this topic is related to the specialist who performs it and the learning curve in such a rare pathology. The gastroenterologist has to be expert in interventional endoscopy and have special skills in surgery, an excellent knowledge in anatomy and the strength to manage the complications. Considering the low rate of adverse events and the efficacy, as a team already performing POEM, we believe that this is the therapy of the future for achalasia.

Abstract

Peroral endoscopic myotomy (POEM) is a new endoscopic treatment for achalasia. Compared to the classical surgical myotomy, POEM brings at least the advantage of minimal invasiveness. The data provided until now suggest that POEM offers excellent short-term symptom resolution, with improvement of dysphagia in more than

Tantau M, Crisan D. Peroral endoscopic myotomy: Time to change our opinion regarding the treatment of achalasia? *World J Gastrointest Endosc* 2015; 7(3): 237-246 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v7/i3/237.htm> DOI: <http://dx.doi.org/10.4253/wjge.v7.i3.237>

INTRODUCTION

The loss of inhibitory innervation of the lower esophageal sphincter (LES) resulting in inadequate relaxation and higher baseline pressures of the LES defines achalasia. Another feature of achalasia is the absence of esophageal peristalsis, these pathogenic modifications explaining the clinical complaints such as regurgitation, dysphagia, retrosternal pain and weight loss. Achalasia has an incidence of 1/100000 per year, which places this disease in the area of rare pathologies. Otherwise, achalasia is the most frequent primary non malignant disease of the esophagus^[1].

Although no treatment with curative intention has been identified, some palliative methods comprising medical, endoscopic and surgical methods have been proposed, all aiming to lower LES pressure. Medical treatment with nitrate and calcium antagonists has proved to have poor efficacy and significant side effects^[2-4]. However, some of the medical methods such as smooth muscle relaxants are still used for chest pain relief in patients with vigorous achalasia. Of the endoscopic treatments, Botox injections and pneumatic dilatation (PD) have been traditionally used. Botox injections at the gastroesophageal junction (GEJ) are initially successful in over 90% of patients, but the effects only last for 6-9 mo. Botox injections are therefore generally reserved for elderly patients or poor surgical candidates^[5]. Pneumatic dilatation is the nonsurgical technique with the highest success rate^[6].

Surgical myotomy was originally reported by Heller in 1913 and consisted of 2 longitudinal incisions of approximately 8 cm on the anterior and posterior esophageal wall, the complete release of the LES being mandatory to achieve complete relief from achalasia symptoms. Later, bilateral myotomy was modified to a single myotomy. One of the limitations and failures of surgical myotomy is gastroesophageal reflux disease (GERD), which was reported in up to 30% of cases, resulting in an additional antireflux procedure, such as fundoplication.

A multicenter study recently published demonstrated no significant differences in clinical success between PD and laparoscopic Heller myotomy (LHM) with fundoplication at a 2 year follow-up^[7]. Although these results are no longer available when it comes to a longer follow-up, the failure rate of PD remaining at 50%-60% promotes LHM as the treatment of choice in young patients and in those without special contraindications for surgery^[6].

Considering these facts, a new endoscopic technique, the peroral endoscopic myotomy (POEM) that combines the surgical element of a controlled myotomy with the minimal invasiveness of endoscopic approach, imposes itself as a real alternative in the treatment of achalasia^[8].

ENDOSCOPIC MYOTOMY

The endoscopy myotomy as a treatment option

in achalasia was first described in 1980^[9]. A limit of this first report was the use of direct incision of the mucosa, which was considered unsafe and unreliable, so it was abandoned. Later, the technique of endoscopic myotomy through a submucosal channel was described in an animal model^[10,11]. Pauli was the first who described the crossing of gastroesophageal junction and esophageal cardiomyotomy^[12]. Based on this experimental background, Inoue refined the technique for clinical application in humans, namely POEM^[13,14].

During POEM, the muscle layer is intentionally dissected and divided through a submucosal tunnel. Mucosa works as a strong barrier to isolate gastrointestinal lumen from the mediastinum or peritoneum. If the mucosa is kept intact, neither peritonitis nor mediastinitis can occur. Complete endoscopic myotomy was first used in a clinical experience together with the development of the POEM.

POEM PROCEDURE

Indications, contraindications

It is generally recommended that teams beginning a POEM program should do it with approval from an institutional review board and after a learning curve completion. Age under 18, previous esophageal or mediastinal surgery and morbid obesity were previously considered exclusion criteria but are no longer valid today. Fungal infection or heavy esophageal loading with food are also considered contraindications but they can be eventually overcome. A real contraindication for POEM remains the inability to undergo general anesthesia^[15] but there are some cases in which POEM has been performed without general anesthesia. POEM is considered to be a safe and effective alternative to the surgical approach in achalasia. The role of POEM in the treatment of other esophageal motor disorders such as diffuse esophageal spasm (DES), non-relaxing hypertensive LES and nutcracker esophagus is still under debate. Also, its role in treating patients with prior conventional therapies for achalasia, in the final stages of achalasia, in children, the elderly and in patients with significant comorbid diseases is still not clear. However, the first reports on this topic are optimistic regarding the benefit of POEM in these pathologies^[8,16].

PREOPERATIVE INVESTIGATIONS

On admission to hospital, all patients diagnosed with achalasia complete a standardized validated symptom assessment form, according to the Eckardt classification. Based on the calculated score, the patients are included in different classes of severity. All patients undergo extensive preoperative investigations such as an esophagogastrosopy, barium swallow study and a pH study useful for the diagnosis of an asymptomatic reflux. In the diagnosis and classification

of achalasia, an essential tool is high resolution manometry.

According to the manometric measurements, achalasia is classified into 3 subtypes (Chicago classification)^[17]: (1) type I (classic achalasia) defined as mean integrated relaxation pressure (IRP) > 15 mmHg and when peristalsis has 100% failed; (2) type II (achalasia with compression) as mean IRP > 15 mmHg, abnormal peristalsis, panesophageal pressurization with \geq 20% of swallows; and (3) type III as mean IRP > 15 mmHg, abnormal peristalsis, fragments of distal peristalsis or premature (spastic) contractions with \geq 20% of swallows preserved.

A group of researchers^[18] have elaborated a new endoscopic classification of achalasia based on three structures: multi-ring, crescent-like and diverticulum structure, named Ling classification. They divided achalasia into three types: type I, smooth without multi-ring, crescent-like structure or diverticulum structure; type II, with multi-ring or crescent-like structure, no diverticulum structure; and type III, with diverticulum structure. Type II and III were also classified into three subtypes (II a, II b, II c; III 1, III r and III 1r). The authors concluded that patients classified as type I and II a patients can be recommended for POEM. Patients included in class II b are at risk of mucosal damage so they might be considered for POEM, but cautiously. This classification needs further confirmation.

Preoperatively, all patients are recommended to have a liquid diet for at least one day before the procedure and some endoscopists perform an upper endoscopy the day before POEM to wash out the esophagus prior to the intervention. Patients may receive oral antimycotics preoperatively to treat any potential esophageal *Candida* overgrowth. A prophylactic dose of antibiotics was reported to be given before the procedure. Some authors reported the administration of dexamethasone at the start of the procedure to minimize mucosal edema, which will eventually make the closure of the mucosa more difficult, but this is not clearly stated^[19].

TECHNICAL ASPECTS OF POEM

Set up and positioning

The procedure is usually done in the operating room under general anesthesia with endotracheal intubation. The gastroscope used for POEM is a standard one. Some authors use a large working channel endoscope with water jet function, but a slim diagnostic scope can be more suitable sometimes for crossing an extremely narrow GEJ. A transparent distal dissecting small cap or an oblique cap can be used at the tip of the endoscope. In order to avoid mucosal laceration at the mucosal incision site during POEM, an overtube might be placed for stabilization of the scope. Another important device to use during this procedure is the carbon dioxide (CO₂) insufflator, which helps to reduce the risk of

complications related to air insufflation (pneumothorax, pneumoperitoneum, embolism and subcutaneous emphysema). The air supply button should expressly be closed during the procedure, even when the CO₂ insufflator is on. A thorough cleaning of the esophageal lumen is done before the beginning of the intervention. Sterile saline should be used during the creation of the submucosal channel given the potential mediastinal or peritoneal entry. Communication with the anesthesia team is essential as the patient may develop tension pneumoperitoneum and may require a decompression of the pneumoperitoneum with a Veress needle^[19].

EQUIPMENT REQUIRED FOR POEM

Submucosal tunneling and myotomy are performed commonly using a triangle tip knife (TT knife) with three angulations which spreads the energy towards a wide circumferential range^[19]. A high frequency electrosurgical energy generator is required that determines a spray coagulation during tissue dissection in a noncontact manner. It can be effectively used in combination with a special knife, *e.g.*, a TT knife, a hook knife, a water jet or hybrid knife for both submucosal dissection and myotomy^[20]. Additionally, for the hemostasis of large bleeding vessels, a monopolar coagulating forceps might be useful during dissection^[20].

POEM PROCEDURE

The following technical details of POEM are consistent with those from original reports^[2,13,14,19].

General anesthesia

Most frequently, POEM is performed with the patient in a supine position, intubated, under general anesthesia. CO₂ insufflation avoids the risk of air-related complications. CO₂ insufflation does not eliminate the risk of gas entry in the mediastinum or abdomen. It does, however, greatly reduce it because CO₂ is rapidly reabsorbed. The air feeding button will remain closed during POEM. The upper abdomen will be checked from time to time during the whole procedure and if the abdomen is excessively distended, an abdominal wall puncture will be performed in order to prevent abdominal compartment syndrome.

Submucosal tunneling

Mucosal entry: Initially, the distal end of the dissection is marked with methylene blue when performing retroflexion in the stomach. Then, an esophageal mucosal lift is performed with a saline injection containing a small amount of methylene blue or indigo carmine on the right anterior side of the esophageal wall. This is followed by a longitudinal mucosectomy of 1-2 cm. It has to have a longitudinal orientation as transverse incisions are nearly impossible to close. Once the submucosal space is entered, the introduction

of the scope in the submucosa is facilitated by the use of a biliary stone extraction balloon. Then, a dissection fenestrated cap is placed on the tip of the scope for the progression in the submucosal space. A tunnel in the submucosa is created using a combination of spray coagulation, CO₂ insufflation and blunt dissection. The separation of the mucosa from the muscle layer is facilitated by repeated injections of the lifting solution. Researchers have tried to improve the technique of submucosal dissection by using a gel that has the capacity of auto-tunneling^[20]. Further studies are needed to confirm the efficacy of this method. The submucosal tunnel should be extended beyond the GEJ for about 2 cm into the proximal stomach.

Identification of GEJ

It is important to correctly identify the GEJ for an adequate myotomy on the gastric side. There are some signs that can be helpful for finding the GEJ: length of insertion of the endoscope, the presence of palisading mucosal vessels, and the transitory increase and later decrease in the resistance of dissection when passing the LES. The increased thickness of the circular muscle bundles of the LES and the yellowish appearance of the submucosal cardial space are an important mark for GEJ. Finally, the discoloration of the cardial mucosa overlying the submucosal tunnel as seen upon retroflexion of the scope in the lumen of the stomach allows the estimation of the distance from the GEJ^[19].

Circular muscle myotomy

The circular muscle bundle usually starts to be dissected two centimeters distal to the mucosal entry point in the submucosal tunnel. The progression of the dissection is important as both the mucosa and the longitudinal muscle layer should be preserved. The specialists observed that the standard length of myotomy should be more than 10 cm (12 cm on the esophageal side and 2 cm below the GEJ), with an average of 16 cm, but Inoue reported a myotomy length of up to 25 cm^[19]. Given the high incidence of GER post-POEM, there is a tendency to decrease the length of the myotomy, except in cases of vigorous achalasia where a longer myotomy is needed. This tailored approach is facilitated by a new endoluminal imaging probe that measures the GEJ distensibility before and after the selective myotomy^[21].

There are some groups of researchers that have compared the full thickness myotomy with a circular muscle myotomy. They concluded that full thickness myotomy improved the procedure time without a significant increase in the procedure-related adverse events or clinical reflux complications. Still, the dissection of the circular muscle layer is generally recommended^[22].

Circular muscle dissection advances from proximal

to distal and the plane of dissection should be maintained correctly. The confirmation of complete myotomy is immediately provided by the facile passage of the scope through the EGJ at the end of myotomy. When reaching the LES, the dissection of all muscle bundles responsible for achalasia should be performed. No anti-reflux procedure is required after the POEM procedure because the external structures of LES are preserved. After completion of the myotomy, the complete relaxation of LES is endoscopically confirmed by the retroflex view of the cardia.

In cases of previous surgical failure, posterior myotomy is recommended to avoid the access to the scar site from the previous surgery.

Closure of mucosal entry

The stomach should be emptied of fluid and gas before closing the mucosa and an antibiotic (*e.g.*, gentamycin) should be spread into the submucosal tunnel^[19]. The mucosal entry site, which is usually up to 3 cm long, is closed with endoscopic clips from the distal to proximal end with a distance of a maximum of 3 mm between clips. A few alternative closure methods have been described such as over-the-scope clips (OTSC)^[23] and fibrin sealants in the case of perforation of the gastric cardia^[24]. Another option described for mucosotomies that cannot be closed is a covered stent^[25]. Lately, an endoscopic suturing device with a two layered closure of esophagotomy (OverStitch) has proved to be a good alternative to clips in difficult situations.

Postoperative care

Patients are kept *nil per os* the day after the procedure and they should receive an intravenous proton-pump inhibitor immediately after the end of procedure. The intravenous therapy can be subsequently changed to oral treatment once a *per os* diet is allowed. A gastrografin esophagram should be performed the next day to rule out a mucosal defect and to ensure adequate opening of the GEJ post myotomy. If there is no evidence of radiological complications, the patient can be discharged after 24 h of hospital stay, with recommendations of a liquid diet for one week. There is no consensus for a "second look" EGD within the next days following POEM as it often does not change the management of these patients^[16]. As the experience in POEM grows, there are some authors that have reported the release of the patients from hospital on the same day after a normal postoperative contrast esophagography^[26].

A 6 mo follow-up is performed after POEM. Patients should undergo follow-up manometry, pH study and esophagogastroscopy. The long-term follow-up consists of performing an upper endoscopy every 5 years in all achalasia patients, given the slightly increased risk for esophageal carcinoma^[27].

RESULTS FROM THE DATA PUBLISHED UNTIL NOW-POEM FOR THE TREATMENT OF ACHALASIA

Effectiveness of POEM

The results obtained after treating achalasia can be assessed using clinical data and technical features. The decrease of Eckardt score under 3, the lowering of LES pressure by more than 50% and the improved aspect of barium esophagogram regarding the time of esophageal emptying can define an efficient therapy^[28].

The first clinical study performed on a database of 17 patients was published by Inoue *et al.*^[13]. Blunt dissection combined with electrocautery were used to achieve the dissection of the circular muscle layer. The site of mucosal dissection was closed with endoclips and the procedure was completed in all patients. Regarding complications, pneumoperitoneum occurred in one patient, successfully treated using a needle to puncture the abdominal wall. No case of emphysema was reported postoperatively and no long-term complications occurred. The dysphagia symptom score was significantly reduced (from 10 to 1.3; $P = 0.0003$) and the resting LES pressure decreased from 52.4 to 19.8 ($P = 0.0001$) after POEM.

Since then, new studies have been conducted on the performance of POEM for achalasia, which have confirmed the high success rate of this technique^[13,29-44] (Table 1).

The majority of studies published on this theme reported a successful therapy in more than 80% of patients, with significant reductions in the Eckardt score and LES pressure. There were a few studies assessing the efficacy of POEM only with a barium esophagogram, the majority using the decrease of pressure as an objective assessment of treatment. Still, there are new methods promising a high quality evaluation of POEM efficacy, such as EndoFLIP (Endolumenal Functional Lumen Imaging Probe), which provides a quantitative assessment of luminal patency and sphincter distension. EndoFLIP was tested for POEM procedure and surgical myotomy. A similar improvement in EGJ distensibility was demonstrated for both methods. The intraprocedural use of FLIP can be predictive of postoperative symptomatic outcomes, providing evidence that FLIP can be used as a calibration tool during therapeutic procedures for achalasia^[45,46].

POEM compared to LHM

As a surgical approach in achalasia, including the relatively new experience with an endoscopic approach, has been used for a number of years, there are already some studies that have compared the efficacy, time of surgery and complications according to these two types of treatment. Teitelbaum *et al.*^[46] analyzed a group of 17 LHM vs a group of 12 POEM patients using timed barium esophagograms before

and after the procedure. Both groups had improved column heights after treatment at 1, 2 and 5 min. There was no difference between the procedures in changes from baseline column height. Both operations resulted in a decreased esophageal width and less angulation between the esophageal body and esophagogastric junction. The authors concluded that POEM and LHM have similar anatomical and functional results in the short term. Ujiki *et al.*^[47] also compared POEM with LHM in 18 vs 21 patients and he observed that operative time, myotomy length and complication rates were equal. After treatment, pain differed significantly (POEM 3.9 ± 0.6 vs LHM 5.7 ± 0.4 , $P = 0.02$ for the visual analog score) and analgesic use was also lower after endoscopic therapy (POEM 26.0 ± 13.7 mg vs LHM 90.0 ± 48.5 mg morphine, $P = 0.02$). Return to activities was significantly faster in the POEM group (2.2 ± 0.6 d vs 6.4 ± 1.0 d, $P = 0.03$). Postoperative dysphagia and Eckardt scores were not different in the two groups. Different results were reported regarding the pain and analgesia by Hungness *et al.*^[34]. They observed that pain scores were similar upon post-anesthesia care unit arrival and on postoperative day 1, but were higher at 2 h for POEM patients (3.5 vs 2 , $P = 0.03$). The operative times were shorter for POEM (113 vs 125 min, $P < 0.05$) and estimated blood loss was less (≤ 10 mL in all cases vs 50 mL, $P < 0.001$). In terms of efficacy, POEM and LHM appeared to have similar perioperative outcomes. Two other American and European studies reported no differences between the two methods regarding the efficacy and safety^[26,48].

POEM for refractory achalasia in the setting of prior interventions

Sharata *et al.*^[49] analyzed the outcomes of POEM in 12 patients (9 achalasia) in the setting of prior endoscopic interventions. POEM was successfully completed in all patients. The improvement of symptoms was achieved in all patients, based on the Eckardt score from 5 to 1 after POEM. There were no differences regarding perioperative outcomes when compared to POEM performed in patients without previous endoscopic intervention. A case of intramural bleeding was reported and one of dehiscence at the place of mucosotomy. The authors concluded that previous endoscopic therapies do not change the outcomes and complications with POEM. Another study compared 21 patients with failed pneumatic dilation with 30 patients without prior treatment, both groups treated subsequently with POEM. For patients with a failed pneumatic dilation, a significant improvement in the Eckardt score, LES pressure and barium esophagogram was observed after POEM. Regarding the operation time, the patients in the group of previously failed pneumatic dilations had a significantly longer procedure compared to patients without previous treatment of achalasia. The outcomes in terms of efficacy were similar in both groups^[50].

Table 1 Efficacy of peroral endoscopic myotomy-data from literature (adapted after^[27])

Ref.	n	Eckardt score (before/after)	LES pressure (before/after)	Efficacy	Time of follow-up (mo)	Patients with recurrent dysphagia
Inoue <i>et al</i> ^[13]	17	10/1.3	52.4/19	100%	5	0
von Renteln <i>et al</i> ^[30]	16	7.8/0.7	27.2/11.8	94%	3	1
Costamagna <i>et al</i> ^[31]	11	7.1/1.1	45.1/16.9	100%	3	0
Swanstrom <i>et al</i> ^[32]	18	6/0	45/16.8	94%	6	1
Ren <i>et al</i> ^[33]	119	-/<3	29.4/13.5	91.7%	10.4	-
Hungness <i>et al</i> ^[34]	18	7/1	19/9	89%	6	2
Inoue <i>et al</i> ^[35]	300	6.13/1.33	27.3/13.4	98%	12	5
Chiu <i>et al</i> ^[36]	16	5.5/0	43.6/29.8	100%	3	0
Lee <i>et al</i> ^[37]	13	6.4/0.4	30.3/15.3	100%	6.9	0
Minami <i>et al</i> ^[38]	28	6.7/0.7	71.2/21	100%	16	0
Verlaan <i>et al</i> ^[39]	10	8/1	20.5/6.8	-	16	-
Stavropoulos <i>et al</i> ^[40]	66	7.9/0.2	42.5/15.4	96%	13	2
Zhou <i>et al</i> ^[41]	205	Relief in 199/205	-	97%	8.5	3
Von Renteln <i>et al</i> ^[42]	70	6.9/1	27.6/8.9	82%	12	9
Teitelbaum <i>et al</i> ^[43]	41	7/1	22/9	92%	12	-

LES: Lower esophageal sphincter.

When analyzing the surgical Heller myotomy, the persistence of symptoms or the recurrence of them was reported in approximately 10%-20% of patients after 2 years of follow-up^[7]. The team conducted by Zhou *et al*^[51] published their experience in performing POEM after 11.9 years from primary HLM. The therapeutic efficacy was proved in 11/12 patients with a decrease of the Eckardt score under 3 and a significant improvement of LES pressure. Non-serious complications were reported: one case of mucosal perforation at GEJ managed endoscopically, one case of pneumoperitoneum that needed decompression with needle, and one patient requiring a chest tube for symptomatic pneumothorax.

Although the optimal therapy for these patients is not standardized yet, the authors suggested that POEM is feasible and has excellent results in terms of symptom relief.

Another report of 10 cases was published regarding the use of POEM after surgical myotomy for recurrence of symptoms. A significant decrease in LES pressure after rescue POEM was reported after a follow-up of three months, without complications. They concluded that short-term results of POEM after surgical myotomy were optimistic but long-term results are to be confirmed^[52].

A very recent article studying the results of POEM after endoscopic and surgical treatment for achalasia was published. The authors reported excellent results in forty cases of POEM after prior endoscopic or surgical therapies. No differences were found with respect to the short-term outcomes and complications. The authors concluded that POEM is a reliable alternative to surgical techniques but longer follow-up will reveal the real results^[53].

ADVERSE EVENTS IN POEM

The rate of serious adverse events of POEM, obtained from the data available until now, is low. The data

we are discussing are based on information from the IPOEMS survey^[16]. The most frequent complications reported until now are CO₂ retention, capnoperitoneum and mediastinal exposure^[27].

Intraoperative adverse events

The risk of aspiration during intubation can be prevented by standard airway protection with a rapid induction time and frequent aspiration of mouth contents. Aspiration as a complication occurs very rarely (< 0.1%)^[16]. As we already mentioned in the technique description, the use of CO₂ as the insufflation gas is extremely important. The occurrence of complications related to air or CO₂ insufflation can be prevented if the insufflations are used sparingly when creating the submucosal channel. In less than 10% of cases, a mucosal perforation or bleeding may occur. Regarding inadvertent perforations, as their occurrence is more frequent in full thickness myotomies during POEM, a more robust closure has to be executed^[54]. If a lesion of the mucosa occurs during POEM, a tight closure of the breach should be performed using clips in order to prevent the intraluminal content reaching the mediastinum.

Bleeding can occur especially at the distal part of dissection. It is usually controlled with coagulation using the tip of the knife but it is important to have electro-surgical hemostatic forceps for larger bleeding vessels. Some authors reported the use of the endoscope, removed from the submucosal tunnel and advanced in the lumen for compression at the bleeding site.

Regarding the complications related to CO₂ insufflation, physiological effects were reported in some studies. Subcutaneous emphysema may occur in a significant manner in up to 15% of cases, but this is usually well tolerated. Capnothorax is rare (less than 5% of cases) and it is also well tolerated; however, if there are signs of hemodynamic instability, a needle for thoracostomy should be placed to prevent tension

pneumothorax. Capnoperitoneum occurs in up to 50% of the cases but it is clinically insignificant^[28].

Postoperative adverse events

Mediastinitis was the most dangerous complication after POEM, due to an esophageal leak. The incidence of mucosal lesions that leads to leakage has been remarkably low (0.2%) and no severe consequences or deaths have been reported. The few cases reported with leaks were drained surgically, without complications^[40,52].

Postoperative bleeding also has a low prevalence. The IPOEMS reported a rate of 1% for bleeding^[16], with rates of 0.7%^[55], 3%^[26] and 7%^[44] in three prospective series. The management of the bleeding complications was performed conservatively using transfusions as required and clinical observation, but there were some cases that required endoscopic re-intervention with hemostasis or Blakemore tamponade^[33,56].

Cardiopulmonary complications are not frequent, although there was one case reported of aspiration pneumonia that required prolonged postoperative recovery^[16].

Late adverse events

Incomplete myotomy and GERD are the main sources of treatment failure. The early studies reported a low prevalence of GERD based on symptoms but later studies indicated a higher prevalence of reflux disease, ranging between 20% and 46% after POEM, revealed by endoscopic findings (erosive esophagitis) or abnormal pH study^[12-16,18,20-22,24]. The prevalence of GERD after POEM based on pH studies is similar to that reported in large prospective trials after a Heller myotomy with fundoplication^[55,57,58].

POEM IN OTHER MOTOR ESOPHAGEAL DISEASES

There are some short reports in small groups of cases with hypertensive motility disorders of esophagus treated with POEM. The efficacy of POEM in patients with diffuse esophageal spasm^[39,59-61], hypertensive LES^[16,62], type III spastic achalasia^[1,13,14,16], nutcracker esophagus^[38] and jackhammer esophagus^[63] has been studied. It has been suggested that pain responds less well to POEM than dysphagia does^[16]. An interesting remark is related to a low POEM efficacy in patients with diffuse esophageal spasm and type III achalasia but the results observed in hypertensive LES and nutcracker esophagus were optimistic. Longer esophageal myotomy seems to be indicated in diffuse esophageal spasms that are characterized by long spastic segments in the distal esophagus. In the same respect, POEM may be more useful than LHM in motor esophageal disorders as the endoscopic approach allows the proximal extension in the body of the esophagus.

LEARNING CURVE IN PERFORMING POEM

POEM is a treatment for a rare disease, the low prevalence contributing to the difficulty of teaching. The procedure meets the principles of natural orifice transluminal endoscopic surgery (NOTES) and interventional endoscopy. It is a demanding procedure, implying potentially serious adverse effects that should be performed only in specialized centers by experts in interventional endoscopy or surgeons who are skilled in endoscopy. The procedure requires specific knowledge, judgment, technical skills and training, the ability to recognize anatomy and maintain orientation.

The team performing the procedure must be familiar with esophageal pathology, with peculiarities of EGJ, with the technique of submucosal dissection and with the management of the most frequent complications. A learning curve of approximately 20 cases has been proposed to accomplish the training period in POEM for an experienced endoscopist^[61]. It has been proved that the length of the procedure and the incidence of inadvertent mucosotomies becomes constant after 20 cases^[61].

Training in the laboratory on animal or cadaver models may facilitate the time for the acquisition of skills necessary to perform a POEM. Proctoring at first cases is also necessary. In a meta-analysis published recently, POEM operators pursued preclinical training before a human POEM in 10 of 16 centers analyzed. Most centers used live animal training with fewer centers using *ex vivo* models or cadavers. The extent of preclinical training varied widely (total hours spent on preclinical training ranged from 12 to 154 h). Proctoring was used in 9 of 16 centers in the first cases of a human POEM. The authors mentioned a number of proctored cases ranging between 1 and 7.

There are some studies published focusing on the learning curve of POEM. Kurian *et al*^[61] analyzed the learning curve for their first 40 POEMs. The outcomes were assessed using the time of procedure and incidence of perforations. The learning curve seemed to reach a plateau at around 20 procedures. Another study observing the accidental mucosotomies and the number of clips required as a means for acquiring the ability of performing the POEM well demonstrated a learning curve of 7 procedures. The myotomy time was also acquired during these procedures but the tunneling time was not reached during this short practice^[64]. Submucosal tunneling seems to be the most challenging part of POEM, with the longest learning curve, but in this study there were not enough patients to analyze the necessary number of procedures for a submucosal tunneling without adverse events.

POEM IN CHILDREN AND THE ELDERLY

A special concern regarding POEM was related to the feasibility of this procedure in patients with

age extremes. Successful therapy was reported in children aged 3 and also in the elderly, the highest age reported being 97. These results encourage us to believe that POEM is a feasible treatment option in different patients irrespective of age, if the patients are selected properly^[41,46,65,66].

POEM IN PATIENTS WITH COMORBIDITIES

The majority of experts consider that POEM is not indicated in patients with a history of cirrhosis with portal hypertension, especially in the presence of varices. Severe coagulopathy could be a contraindication as well as prior interventions resulting in significant submucosal fibrosis, such as esophageal irradiation and ablation therapy. Pulmonary fibrosis with respiratory failure makes POEM difficult to recommend in patients with this type of pathology^[16].

CONCLUSION

POEM appears to be a feasible endoscopic therapy for achalasia with excellent short-term clinical results and improvement in manometric outcomes. Compared to the classical gold standard approach (surgical myotomy), it is a minimally invasive procedure with good outcomes and a safe profile. On the other hand, POEM is a sophisticated and technically demanding procedure that should be performed only by experts in interventional endoscopy and developed in equipped technical centers with numerous cases of achalasia. Further prospective randomized trials are required to compare the effectiveness of POEM with other actual therapies and to establish its long-term outcomes for the management of achalasia.

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P- Reviewer: Bo Y, Pauli EM, Tsai HH S- Editor: Tian YL
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