12 The Endoscopic Treatment of Esophageal Motility Disorders

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Introduction

Esophageal dysmotility disorders include several benign diseases of the esophagus that impair adequate conduction of the food bolus to the stomach. Esophageal food transport may be didactically divided into four phases. The first phase is the accommodation—when the esophagus receives and accepts the bolus from the oropharynx. The second phase is the compartmentalization—when medullary programmed peristalsis of the proximal esophagus leads the bolus into the distal esophagus. The third phase is the esophageal emptying—when the bolus is expelled from the esophagus and into the stomach that is mainly mediated by post-transition zone myenteric plexus programmed peristalsis. The final phase is the ampullary emptying—when the lower esophageal sphincter (LES) returns to its preperistaltic state, that is closed, shortened, and intrahiatal [1]. Abnormalities in any of the aforementioned phases may elicit symptoms.

High-resolution manometry (HRM) findings were recently standardized by the Chicago Classification that restructured the classification of the esophageal motility disorders. It has gained broad acceptance worldwide while it divides disorders into major (achalasia, esophagogastric junction [EGJ] obstruction, distal esophageal spasm, jackhammer esophagus, absent contractility, end-stage achalasia) and minor ones (ineffective esophageal motility and fragmented peristalsis). The HRM is based on three key metrics: the integrated relaxation pressure (IRP), the distal contractile integral (DCI), and the distal latency (DL) [2]. The combination of different

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abnormalities in those three topographic metrics is indicative of specific motility disorders [3].

Achalasia is the main esophageal dysmotility disorder characterized by degeneration of the inhibitory myenteric ganglion cells of the esophagus [4]. Its central condition is impaired LES relaxation. The HRM helps to identify three types of achalasia based on the other pressure parameters: type I, no esophageal peristalsis; type II, pan-esophageal pressurization; and type III, premature spastic distal contractions. Furthermore, preservation of the peristalsis in the context of an impaired LES relaxation suggests a fourth phenotypic diagnosis: outlet obstruction such as postoperative pseudoachalasia [5]. That is particularly important since the best therapeutic approach and response to treatment may differ according to the subtype of achalasia [6].

It is a rare disease with an incidence of around 1.6 per 100,000 and prevalence around 10.8 per 100,000 [7]. More than 90% of patients suffer from dysphagia but other frequent symptoms are regurgitation, heartburn, and chest pain [8]. The HRM is the main diagnostic tool but upper endoscopy and upper contrast studies may also corroborate and help classify the severity of the disease, especially in an altered anatomy context [3, 9, 10].

The exact physiopathology of the achalasia is not well understood but viral infection, genetic inheritance, and autoimmune diseases have been proposed as triggers for esophageal achalasia [4]. In Southern countries, such as Brazil, a parasite called *Trypanosoma cruzi* transmitted by an insect—the barbeiro—may infect the esophagus, destroy esophageal ganglia, ultimately leading to the chagasic achalasia [9, 11]. Since no other obvious etiologic causes for achalasia have been unequivocally identified to date, all but chagasic achalasia are still referred to as idiopathic.

In spite of the etiology, the classic gold-standard treatment for achalasia is the surgical Heller's myotomy, typically associated with a fundoplication to avoid long-term gastroesophageal reflux disease (GERD) [9]. However, several endoscopic techniques have been reported to address achalasia, each with different efficacy and safety profiles. Botulinum toxin (BTx) injection at the esophagogastric junction (EGJ), pneumatic dilation (PD) with large balloons, and most recently the peroral endoscopic myotomy (POEM) are the main endoscopic treatment modalities [12–14]. The aim of this chapter is to review and summarize the current role of these endoluminal approaches to treat achalasia and other dysmotility disorders.

Botulinum Toxin (BTx) Injection

The BTx is a neurotoxin that acts through a strong binding to the presynaptic cholinergic-nerve terminals, ultimately inhibiting the acetylcholine release from nerve endings [15]. It impairs muscular contractility and may also lower smooth muscle tone in the gastrointestinal (GI) tract [16]. In 1994, Pasricha et al described the first human use of the BTx injections in the EGJ to treat achalasia. Ten patients with achalasia underwent one to three sessions of BTx injections. Six patients presented clinical improvement sustained up to 1 year, three had an initial improvement but relapsed within 2 months, and one did not improve (treatment failure) [16].

A posterior study from the same working group was published 2 years later. Among the 31 patients who underwent BTx injections, 28 improved initially but only 20 had a sustained improvement beyond 3 months (so-called responders). Ultimately, 19 out of the 20 responders relapsed at a median follow-up of 468 days (153–840 days) [12].

However, in time, robust data from controlled randomized trials succeeded in proving the superiority of either the surgical approach (Heller's myotomy) or the pneumatic dilation (PD) over the BTx injection. Vaezi et al enrolled 42 patients that were randomly allocated to either BTx injection or PD. The pneumatic dilation carried the same initial failure rate but higher remission rates at 12 months (70% × 32%, $p < 0.05$). Moreover, PD significantly reduced symptom scores, lowered LES pressure and the esophageal barium column height, while BTx resulted only in a reduction in symptom scores [17]. Accordingly, a recent systematic review published in the Cochrane Database included seven randomized studies comparing those two endoscopic modalities. The authors firmly concluded that PD was more effective than BTx in the long term (greater than 6 months) [18].

As to comparisons with the Heller's procedure, Zaninotto et al randomly allocated 40 patients to BTx injections in the EGJ and 40 to surgical myotomy in 2004. Except for slightly lower symptom scores favoring surgery, most results were comparable at 6 months. Nonetheless, 65% of BTx patients recurred at 2 years; thus, the probability of being symptom-free at 2 years was 87.5% after myotomy and 34% after BTx ($p < 0.05$) [19].

Consequently, the transient effect of the BTx diminished significantly its role in the endoscopic armamentarium against achalasia. Currently, most authors consider BTx only for patients not amenable to more invasive procedures such as PD, POEM, or surgery [13, 20].

Pneumatic Dilation

The pneumatic dilation of the LES is usually performed under both endoscopic and fluoroscopic guidance. A prior upper GI endoscopy with esophageal chromoscopy is strongly recommended due to the high risk of squamous cell cancer in achalasia patients [21]. Initially, the distance from the EGJ to the superior dental arch is endoscopically measured and later used to help to position the mid portion of the balloon exactly over the LES. Then, the endoscopist places a large diameter, catheter-based, noncompliant, over-the-scope balloon (Fig. 12.1) across the EGJ using fluoroscopy and the previous measurement. The balloon is gradually inflated using a handheld manometer up to 1.4 psi to reach 30 mm in diameter (Fig. 12.2). Further sessions dilation up to 40 mm may be needed in cases of relapse or poor initial response. This specific technique has been described to have less serious adverse events and mortality than the surgical myotomy [22].

Fig. 12.1 Picture of the handheld manometer and the achalasia balloon

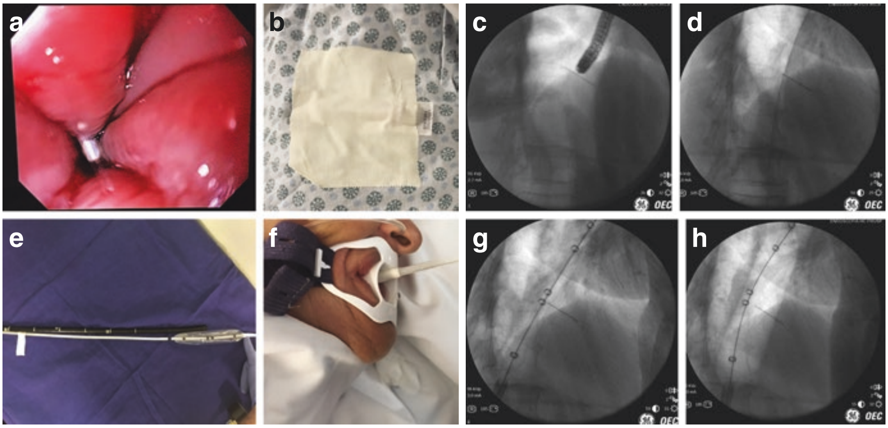

Fig. 12.2 Pneumatic dilation procedure: (**a**) endoscopic identification of the esophagogastric junction; (**b** and **c**) placement of external radiopaque marks at the esophagogastric junction (EGJ); (**d**) placement of the metallic guidewire in the antrum towards the esophagogastric junction; (**e**) marking the balloon with tape according to the distance from the superior dental arch to the EGJ; (**f** and **g**) introduction of the balloon over the wire until both marks match; (**h**) fluoroscopic appearance of the inflated pneumatic balloon

Browne and McHardy published the first description of PD to treat achalasia in 1939 [23] and Benedict EB reported the first comparison of dilation and surgical myotomy in 1964 [24]. Decades later, the good outcomes of the PD rendered this modality a plausible alternative to the surgical myotomy [25, 26].

The most robust article to date is a European multicenter controlled trial comparing the endoscopic dilation and the laparoscopic Heller's myotomy (LHM). Published in 2011, this study enrolled 201 newly diagnosed patients allocated either to PD (n = 95) or to LHM (n = 106) who were followed for a mean of 43 months. The therapeutic success rates (Eckardt score ≤ 3 [27]) for the PD group were 90% and 86% at 1 and 2 years, respectively, while 93% and 90% for the LHM group in the intention-to-treat analysis (p = 0.46). Accordingly, there was no difference between groups regarding LES pressure, the height of the barium-contrast column, and quality of life at 2 years. The perforation rate during PD was 4% and the rate of mucosal tears during LHM was 12% (p = 0.28). This study concluded that there were no relevant differences in terms of efficacy and safety of the PD compared to the LHM [28]. The following study with a 5-year evaluation confirmed those finding at a longer term except for a need for redilation of 25% in the PD group [29]. A recent meta-analysis also reported similar results [26].

As a consequence of the aforementioned data, the endoscopic pneumatic balloon dilation of the LES remains as a relevant alternative to surgical myotomy [20].

Peroral Endoscopic Myotomy (POEM)

The first description of an endoscopic esophageal myotomy was reported in an animal study by Pasricha et al in 2007 [30]. In 2010, Inoue et al published the first human feasibility study describing the POEM in 17 patients [31]. Despite being a recently developed procedure, it has gained worldwide acceptance. Despite the lack of controlled studies, series as large as 1000 patients are currently available, which hardly classify POEM as an experimental procedure [14].

This procedure is usually performed under general anesthesia with the patient in left lateral decubitus or supine position. The first step of the procedure is to measure the distance between the superior dental arch and the EGJ. Around 6 to 10 cm cranially to the EGJ, the operator injects saline with indigo carmine to create a submucosal cushion and then incise the mucosa. Using a cone-shaped cap attached to the end of the scope, the endoscopist manages to enter the submucosal space and dissects this layer caudally up to 2–4 cm below the EGJ. Then, under complete endoscopic visualization and control, the muscularis propria layer of the stomach just below the LES, the LES itself, and the muscularis propria layer of the esophagus are cut in a distal-to-proximal fashion. Finally, the mucosal incision is closed using a sequence of endoclips [32] (Fig. 12.3). Several technical particularities exist among different centers and experts, namely, anterior or posterior wall tunneling [33], full-thickness (circular and longitudinal) or circular-only myotomy [34], and length of the myotomy [35]. However, there is still no consensus among studies on the impact of those technical dissimilarities in short- or long-term outcomes.

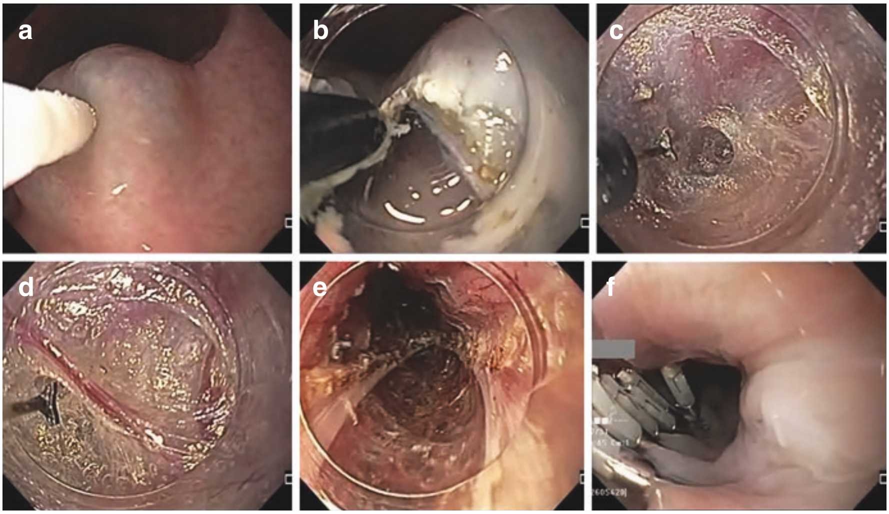

Fig. 12.3 The peroral endoscopic myotomy (POEM) procedure: (**a**) injection at the mid esophagus to create a submucosal cushion; (**b**) mucosal incision; (**c** and **d**) submucosal tunneling; (**e**) full-thickness endoscopic myotomy showing the longitudinal muscular layer completely cut; (**f**) final mucosal clipping. (Gentle courtesy from Dr. José Eduardo Brunaldi)

In spite of the lack of randomized controlled trials (RCTs) comparing POEM to LHM, robust data certify the effectiveness of POEM in most clinical scenarios. In 2015, Inoue et al. reported a series of 500 POEM cases. Approximately 82% of patients had nonsigmoid esophagus but almost 40% had previously undergone treatment for achalasia (PD, BTx injection or LHM). At 2 months, the authors reported significant reductions in Eckardt score (6.0 ± 3.0 vs. 1.0 ± 2.0, $p < 0.0001$) and in LES pressure (25.4 ± 17.1 vs. 13.4 ± 5.9 mmHg, $p < 0.0001$), both sustained at 3 years post-POEM. As a long-term adverse effect, 16.8% and 21.3% of patients presented GERD at 2 months and 3 years, respectively [32].

Although full text is not available yet, a randomized trial including 133 therapy-naïve patients comparing POEM to PD was published in 2017. At 1 year, 92.2% of POEM patients had clinical remission (Eckardt score ≤ 3) versus 70% of PD patients ($p < 0.01$). There were two serious adverse events in the PD group (1 perforation, 1 chest pain requiring admission) and none in the POEM group. However, 48% of POEM patients had esophagitis versus 13% of PD patients ($p < 0.01$) after proton pump inhibitor (PPI) cessation at 1-year follow-up.

Patel et al recently published a systematic review and meta-analysis assessing the efficacy and safety of POEM to treat achalasia. In a noncomparative analysis, the article included 22 studies with a total of 1122 patients. The pooled average pre- and post-POEM Eckardt score were 6.8 ± 1.0 and 1.2 ± 0.6 ($p < 0.01$), respectively. Accordingly, the authors demonstrated reductions by 66% and 80% in the LES pressure and timed barium esophagogram column height, respectively. Three comparative noncontrolled studies were also included in this meta-analysis. Comparisons with LHM showed similar total adverse events rate and incidence of perforation but shorter length of stay and operative time for POEM [36]. Another systematic review exclusively investigated comparisons with LHM. Fifty-three studies enrolling 5834 patients undergoing LHM and 21 articles with 1958 patients undergoing POEM were included. The predicted probabilities for improvement in dysphagia at 12 and 24 months were 93.5% and 92.7% for POEM versus 91.0% and 90.0% for LHM (both p = 0.01). However, patients who underwent POEM were more likely to develop GERD symptoms, erosive esophagitis, and altered pH monitoring compared to LHM. In contrast to the previous systematic review, the authors found the length of hospital stay to be 1.03 days longer after POEM than LHM (p = 0.04) [37]. Nonetheless, there are still no controlled data comparing those two therapeutic modalities but a few ongoing trials shall fill this gap in the near future and might confirm the aforementioned results.

Reliable international experiences have also demonstrated good efficacy and safety profile of POEM to address achalasia in the pediatric population [38], in patients who relapsed or failed primary POEM [39], and to treat cases of failed LHM [40, 41].

The main shortcoming of the POEM is the development of GERD. The destruction of the most important antireflux mechanism without associating a fundoplication ultimately favors gastric content reflux into the distal esophagus. Studies report GERD in up to 46% of patients after POEM [20]. A recent systematic review including 45 studies and more than 4000 individuals compared POEM to LHM in terms of GERD. The pooled rate of esophagitis assessed by upper endoscopy was 29.4% and 7.6% after POEM and LHM, respectively. The pooled rate estimate of abnormal acid exposure at pH monitoring was 39% and 16.8% after POEM and LHM, respectively [42]. Therefore, strict follow-up focused on preventing long-term complications of GERD is strongly recommended for POEM patients.

In an attempt to address this drawback, Inoue et al reported a series of 21 cases associating a NOTES fundoplication with the standard POEM. After performing the full-thickness myotomy, the endoscopist managed to enter the abdominal cavity incising the peritoneum at the anterior wall of the stomach. Using a combination of an endoloop and endoclips, the fundus was retracted at the EGJ thus creating a fundoplication. The authors reported no immediate or delayed complications of the procedure. Accordingly, length of stay and use of analgesia were similar to the conventional POEM. The fundoplication added a mean of 51 minutes to the procedure. At 2 months, 20/21 patients (95%) had a wrap across the EGJ consistent with an intact plication [43]. Despite being the only available study to date describing this technique, the rationale is exciting. Further studies are needed to assess its effectiveness at preventing long-term GERD.

Treatment Options According to the HRM

The introduction of the HRM in the management of esophageal motility disorders allowed the identification of new predictive factors for good response to treatment. The subdivision of types of achalasia is one of the most important among them. In spite of the treatment modality, the type II achalasia has good response rates over 90% in most studies. On the contrary, type III carries the worst outcome: good outcome rates as low as 30% for endoscopic treatments other than POEM and as low as 69% for LHM. Finally, the type I achalasia has intermediate outcomes [6, 44–46].

In fact, since the Chicago Classification was released [2], it was possible to create phenotypes instead of purely labeled diseases, thus allowing guidance according to the topographic finding. In this sense, that is the major advantage of the POEM procedure: the possibility to increase the length of the myotomy as needed and eventually even guide by the HRM findings. Khan et al recently published a meta-analysis pooling data from uncontrolled POEM series and analyzed response rates according to the manometric diagnoses. Contrary to previous data, the authors showed a pooled response rate of 92% for type III achalasia with a mean myotomy length of 17 cm. Moreover, this same treatment provided good responses in 72% of patients with Jackhammer esophagus and in 88% of patients with distal esophageal spasm. Such long myotomy rendering POEM effective in these contexts corroborates the rationale of treating according to HRM topographic findings on a case-by-case basis [47].

In this sense, a very experienced group from Japan created a therapeutic algorithm grouping motility disorders according to specific topographic findings that ultimately define treatment particularities. Tuason and Inoue proposed the categorization of disorders in three groups: group 1 (achalasia type I, type II, and EGJ outflow obstruction), group 2 (type III achalasia), and group 3 (Diffuse esophageal spasm and Jackhammer esophagus). The best approach differs according to the group: group 1 should undergo standard POEM, group 2 should undergo extended myotomy, and group 3 should undergo LES-preserving myotomy of the esophageal body [20] (Fig. 12.4). This algorithm is novel and currently, no controlled data derives from it. Nevertheless, it seems extremely accurate at customizing treatment according to the origin of the disorder.

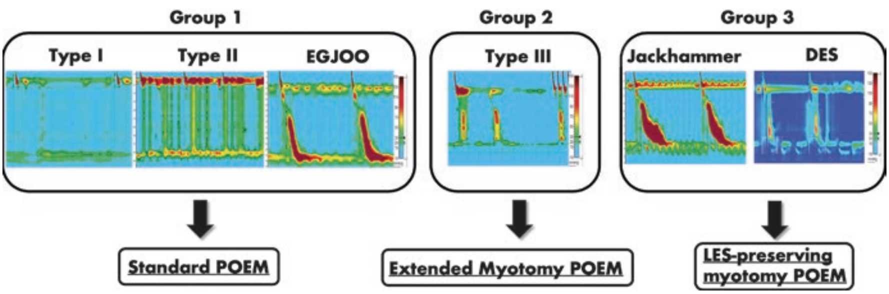

Fig. 12.4 Therapeutic algorithm for peroral endoscopic myotomy according to high-resolution manometry findings. (Gentle courtesy from Dr. Ricardo Brandt and Dr. Leticia Roque). EGJOO esophagogastric junction outflow obstruction, DES diffuse esophageal spasm, POEM peroral endoscopic myotomy, LES lower esophageal sphincter

Once again, controlled data are needed to prove the effectiveness and safety of POEM compared to LHM. In the meantime, robust non-controlled data may support the routine employment of POEM to treat achalasia. Finally, future randomized controlled trials must assess the impact of the aforementioned customization of the endoscopic approach on long-term efficacy. As to other endoscopic treatments, botulinum toxin injection at the EGJ has currently very limited indications but PD is still firmly established as a plausible alternative to surgery especially for type II achalasia.

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