Recent Trends in the Management of Achalasia

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Radical treatment for achalasia is currently unavailable. At present, most palliative procedures are designed to improve the passage of food through the gastroesophageal junction and thereby alleviate symptoms. Drug therapy is of limited, transient effectiveness. Pneumatic dilation (PD) is considered superior to endoscopic botulinum toxin injection (EBTI). The mainstay of surgical treatment for achalasia is laparoscopic Heller myotomy (LHM) with fundoplication, currently considered superior to PD. Per oral endoscopic myotomy (POEM), a “state-of-the-art” procedure for minimally invasive surgery, holds great promise for the future management of achalasia. Definitive conclusions regarding the benefits and risks of currently available treatments for achalasia must await the accumulation of evidence from well-designed clinical trials.

Keywords: achalasia, pneumatic dilation, laparoscopic Heller myotomy, per oral endoscopic myotomy

Introduction

Esophageal achalasia has been ascribed to degeneration of Auerbach’s plexus,1,2 but its cause remains uncertain. Achalasia is characterized by impaired relaxation of the lower esophageal sphincter (LES). Secondary characteristics include elevated LES pressure and the lack of esophageal body peristalsis.3,4 Passage through the gastric cardia is consequently impaired, leading to dysphagia. The incidence of achalasia is approximately one in 100000 individuals annually; the estimated prevalence is 10 in 100000.5 Achalasia can occur at any age, but most commonly develops between the ages of 20 and 40 years.

There appears to be no sex or racial predilection. Progressive dysphagia for solid foods and liquids and chest pain are the main symptoms in more than 80% of patients with achalasia; about two thirds of all patients have regurgitation.6,7 Although it is generally accepted that achalasia is a pre-malignant disorder, the reported risk of squamous cell carcinoma in patients with achalasia is 0 to 140 times higher than that in the general population.8 Leeuwenburgh I et al.9 surveyed a cohort of 448 patients with achalasia for a mean follow-up of 9.6 years. Overall, esophageal cancer developed in 15 (3.3%) patients (10 men). Mean age at the diagnosis of cancer was 71 years (range, 36–90) after a mean follow-up of 11 years (range 2–23) from initial presentation and a mean of 24 years (range, 10–43) from symptom onset. The relative hazard rate of esophageal cancer was 28 (confidence interval, 17–46) as compared with an age- and sex-matched population in the same time frame.

Diagnosis of achalasia in patients who have early-stage disease associated with mild esophageal distension is challenging owing to the apparent lack of distension on endoscopic examination. The disease thus often goes undiagnosed. On the other hand, achalasia should be
suspected in patients who present with food residue and fluid accumulation in the esophagus in the absence of stenosis due to organic causes, such as malignant tumors of the cardia or reflux esophagitis. Although endoscopic examinations currently play a more important role than imaging studies in the diagnosis of upper gastrointestinal diseases, esophagography remains an effective procedure for the diagnosis of achalasia. On esophagography, achalasia is characterized by the presence of impaired passage at the esophagogastric junction, associated with symmetric, smooth narrowing of the region. Accumulation of barium is seen in the body of the esophagus in association with esophageal distension. Attention should also be paid to the curvature or bending of the lower esophagus and the appearance of abnormal contraction waves. Because achalasia is a disorder of esophageal motility, direct evaluation of mobility by esophageal manometry has an important role in the definitive diagnosis. The cardinal feature of achalasia is impaired relaxation of the LES. Secondary changes include elevated LES pressure and the absence of esophageal body peristalsis. Recently, high-resolution manometry (HRM) has been introduced as a new technique for the evaluation of esophageal motility disorders. HRM uses more closely spaced pressure sensors than conventional manometry, enabling the motility of the entire esophagus to be displayed as concrete color images. The new Chicago classification has been proposed to classify esophageal motility disorders on HRM. Achalasia is classified into types I, II, and III on the basis of esophageal body motility.10

Radical treatment for achalasia is currently unavailable. Palliative treatment options include drug therapy, pneumatic dilation (PD), endoscopic botulinum toxin injection (EBTI), surgical therapy, and per oral endoscopic myotomy (POEM). These palliative procedures are designed to improve the passage of solid food and liquids through the gastroesophageal junction and thereby alleviate symptoms. They do not improve impaired relaxation of the LES, the main, underlying cause of achalasia.

**Drugs Therapy**

Drugs that improve impaired relaxation of the LES have been awaited, but have yet to be developed. Currently available drugs, such as short-acting calcium antagonists and nitrates, are used to alleviate dysphagia by lowering LES pressure. Administration of both drugs has been reported to lower LES pressure by 47% to 63%.11 As for the timing of treatment, nifedipine (5–10 mg) or isosorbide dinitrate (5–10 mg) is given 20 to 30 minutes before meals. In general, drug therapy is not that effective against dysphagia and the response is temporary and reversible. Symptoms are thus rarely controlled by drugs alone. Drugs used to treat achalasia often cause adverse reactions such as headache and hypotension, precluding long-term, continuous treatment. Drug therapy is, therefore, reserved for patients not willing or unable to undergo any other procedure, patients awaiting more definitive therapy, or as supportive treatment for patients with refractory chest pain associated with achalasia.

**Pneumatic Dilation (PD)**

PD attempts to decrease LES pressure by forcibly dilating and severing LES myofibers, thereby improving passage disorders. This procedure is less invasive than surgery and can be used for follow-up treatment in patients with recurrence or no response. Dilation dates back to 1674, when Willis used a whalebone bougie to perform the procedure.12 Subsequently, dilation has been performed by various techniques. Recently, a polyethylene low-compliance balloon (Rigiflex Achalasia Balloon Dilator, Boston Scientific, Boston, MA, USA) is most widely used because it is considered safest and most effective. A balloon ≥3 cm in diameter is most often used.13 PD is performed by various procedures, depending on the hospital. With the standard procedure, a guide wire is endoscopically inserted through the esophagus into the stomach. A balloon director is then inserted along the guide wire. The center of the balloon is placed in the esophagogastric junction under fluoroscopic guidance. The balloon is insufflated with air, and the pressure is increased while confirming that the balloon is at the center of the constriction. Dilation is performed until the constriction disappears. With the use of a Rigiflex Achalasia Balloon Dilator, the mean time required to reach the required pressure for PD was reported to be 73 seconds (range, 6–240), with a mean dilation pressure of 10.9 psi (range, 7–18).13

A systematic review by Campos et al. reported a success rate of 84.8% within one month after the procedure. However, success rates steadily declined on longitudinal follow-up. At subsequent evaluations, the success rate was 73.8% at 6 months, 68.2% at 12 months, and 58.4% at 36 months or longer. In addition, 25% of patients required repeat PD.13 Eckardt et al. reported that an LES pressure of 10 mm Hg or less after PD was the most important predictor of the long-term clinical response and
that patients younger than 40 years are less likely to respond to PD.14) On the other hand, Ghoshal et al. reported that poor outcomes were associated with male gender, pulmonary symptoms, absence of chest pain, and failure to achieve a reduction in LES pressure of >50% after PD, but not with age, grade of dysphagia, regurgitation, megaeosophagus, or LES pressure before PD.15) Esophageal perforation was previously a problematic complication of PD, but improvements in balloon materials and other factors have decreased the incidence of perforation to 1.6% on average.13)

### Endoscopic Botulinum Toxin Injection (EBTI)

EBTI in the LES inhibits the release of acetylcholine from cholinergic neurons, thereby lowering both basal and residual LES pressures.16) EBTI is usually performed by injecting 20 to 25 units of botulinum toxin into quadrants, for a total dose of 80 to 100 units. Symptomatic relief or improvement was reported in 78.3% of patients within 1 month after the procedure. However, symptomatic relief steadily declined in subsequent months (70% at 3 months, 53.3% at 6 months, and 40.6% at 12 months or longer).13) EBTI was thus shown to be effective in the short term, whereas additional treatment was required for continuous, long-term effectiveness.17) Another problem is the appearance of antibodies against botulinum toxin. Because of these limitations, EBTI is reserved for patients who are too ill to undergo surgery.18)

### Surgical Therapy

The surgical procedure most widely used to treat achalasia is Heller myotomy, in which the muscle layer of the esophagus is incised from the distal esophagus to the proximal stomach.19) However, one study reported that gastroesophageal reflux develops during long-term follow-up in 48% of patients who undergo myotomy alone.20) A general consensus has been reached that some type of anti reflux procedure should be performed concurrently with myotomy to prevent postoperative gastroesophageal reflux. Technically, anti reflux procedures are easier to perform via a transabdominal rather than a transthoracic approach. Successful outcomes of surgery for achalasia require a good balance between two factors: relief of dysphagia, achieved by decreasing LES pressure by Heller myotomy, and the prevention of postoperative gastroesophageal reflux, achieved by performing an anti-reflux procedure.

Endoscopic procedures for minimally invasive surgical treatment of achalasia date back to 1991, when Shimi et al. described a technique for laparoscopic Heller myotomy (LHM).21) Endoscopic treatment of achalasia has since become more popular. Ancona et al. compared LHM plus Dor fundoplication performed endoscopically with the same procedure performed by conventional open surgery.22) Their results clearly showed that laparoscopic surgery was less invasive. Outcomes were similar for both procedures. Laparoscopic surgery was associated with less postoperative pain, a shorter postoperative hospital stay, and prompter resumption of daily activities after surgery. Douard et al. compared outcomes of the laparoscopic Heller-Dor operation with those of the open Heller-Dor operation in patients with esophageal achalasia.23) The clinical effectiveness of these procedures was shown to be similar in terms of symptomatic relief and the decrease in LES pressure.

### Heller Myotomy

Dysphagia, the cardinal symptom of achalasia, is reduced by Heller myotomy, which decreases cardial pressure. Heller myotomy thus plays an extremely important role in the surgical management of esophageal achalasia. Mattioli et al. intraoperatively measured internal pressure to study the optimal incision length and extent in Heller myotomy.24) They reported that a myotomy with a cut length of 2 cm on the gastric side maintained a LES pressure of 45%. They concluded that a 2-cm incision made distally to the gastroesophageal junction, after making a proximal incision of 5 to 6 cm, played the most important role in decreasing the final LES pressure after the Heller myotomy. Wright et al. compared the long-term efficacy of the standard Heller myotomy, with a cut length of 1 to 2 cm on the gastric side, with that of an extended Heller myotomy, with a cut length of >3 cm. They found that extended myotomy provides excellent dysphagia relief, superior to that obtained with standard myotomy.25) Patti et al. reported that impaired visualization of the gastroesophageal junction might be the principal cause of an inadequate cardiomyotomy.26) Available evidence thus indicates that evaluation of the anterior esophageal fat pad to accurately identify the gastroesophageal junction and a cut length of at least 2 cm in cardiomyotomy are the most important determinants of a successful outcome of Heller myotomy (Fig. 1).

Avoidance of intraoperative injury to the esophageal mucosa is of paramount importance in surgery for achalasia. A systematic review by Campos et al. reported that
the rate of esophageal perforation associated with laparoscopic myotomy was 6.9% on average (range, 0%–33%).\(^{13}\)

The esophageal sphincter and mucosa should thus be carefully stripped during the myotomy, exercising extreme caution not to damage the mucosa. However, because the esophagus has an oblique muscular structure, in addition to internal circular muscles and external longitudinal muscles, particular care should be exercised on dissection of the mucosa and muscularis when making the incision on the gastric side. It is also important to endoscopically confirm the presence or absence of mucosal injury before completing surgery. If the mucosa is injured, the site of injury can be sutured, thereby preventing postoperative complications.

**LHM plus Anti-Reflux Procedures**

Heller myotomy has long been known to carry a postoperative risk of gastroesophageal reflux. Richards et al. compared a group of patients with achalasia who underwent laparoscopic Heller myotomy with a group who underwent laparoscopic Heller myotomy plus Dor fundoplication as an anti-reflux procedure.\(^{27}\) Their results showed that the addition of Dor fundoplication significantly decreased the incidence of gastroesophageal reflux after operation. However, the addition of an anti-reflux procedure to Heller myotomy did not completely eliminate postoperative gastroesophageal reflux. The rate of gastroesophageal reflux after LHM with an anti-reflux procedure has been reported to range from 0% to 44%, with an average rate of 8.8%.\(^{13}\) Caution is required because untreated reflux can become severe, leading to strictures of the lower esophagus and the recurrence of passage disorders. Three representative anti-reflux procedures combined with LHM are briefly described here.

**LHM with Nissen Fundoplication (Fig. 2-a)**

Excellent or good outcomes, especially with respect to preventing gastroesophageal reflux, have been obtained in patients who underwent LHM with Nissen fundoplication. Because Nissen fundoplication is a technique for total fundoplication, it is expected to more effectively prevent reflux than the Dor or Toupet procedures, which are techniques for partial fundoplication. Rebecchi et al. compared the long-term results of LHM plus Dor fundoplication with those of LHM plus Nissen fundoplication in patients with achalasia who were enrolled in a prospective, randomized trial.\(^{28}\) There was no significant difference in instrument-related gastroesophageal reflux between the two groups; however, the rate of dysphagia was significantly higher after Nissen fundoplication than after Dor fundoplication (15% vs. 2.8%; \(p < 0.001\)). Adding Nissen fundoplication significantly increased the pressure and length of the LES as compared with preoperative values. These results showed that Nissen fundoplication is very effective for preventing gastroesophageal reflux but carries a high postoperative risk of severe dysphagia. Consequently, Nissen fundoplication does not seem to be recommended as an anti-reflux procedure, added to LHM.

**LHM with Dor Fundoplication (Fig. 2-b)**

Currently, LHM with Dor fundoplication is the laparoscopic surgical procedure most widely performed to manage achalasia.\(^{29}\) Usually, the left side of the wrap (fundus) is sutured to the cut muscularis on the left side of the esophagus with several sutures. The right side of the wrap (fundus) is then sutured to the cut muscularis on the right side of the esophagus in an identical fashion. The fundoplication is completed by covering the anterior aspect of the cut muscularis. With the Heller-Dor procedure,
leakage of esophageal contents into the peritoneal cavity can be prevented even if the mucosa is injured because the site of injury is covered with the wrap. However, after the Heller-Dor procedure, stress is medially applied to the right border of the myotomy. Thus, fibrosis might develop between the wrap and mucosa, potentially increasing the postoperative risk of residual dysphagia.30)

**LHM with Toupet Fundoplication (Fig. 2-c)**

For performing a posterior partial or Toupet fundoplication, the fundus is pulled to the right through a window created in the posterior aspect of the esophagus. The wrap on the right side of the esophagus is sutured to the cut muscularis on the right side of the esophagus with several sutures. The wrap on the left side of the esophagus is then sutured to the cut muscularis on the left side of the esophagus with several sutures. The esophagus is adequately distended and straightened, and the left and right wraps are then sutured to the diaphragmatic crura. Although experience with the Heller-Toupet procedure is relatively limited, Raiser et al. compared the Heller-Dor procedure with the Heller-Toupet procedure in patients with achalasia who underwent laparoscopic surgery. Their results showed that the Heller-Toupet procedure is associated with a lower risk of postoperative dysphagia.30)

One advantage of the Heller-Toupet procedure is that the wrap around the posterior aspect of the esophagus pulls the anterior wall of the esophagus to the left and right, which opens the myotomy site and produces a sustained decline in LES pressure.

Katada et al. reported that LHM with Toupet fundoplication was an effective procedure in patients with sigmoid-type achalasia because it applied strong inferior traction to the esophagus, keeping it straight.31) Because the Toupet fundoplication is performed after the lower esophagus has been pulled inferiorly and straightened, passage through the cardia is improved, decreasing the risk of postoperative dysphagia. Arain et al. compared outcomes after LHM with partial fundoplication using either a Dor or Toupet procedure.32) They found no significant differences in the physicians’ assessment of postoperative symptom scores and resolution of dysphagia, the patients’ assessment of outcomes, or the postoperative use of proton-pump inhibitors.

**Esophageal Diverticula after Heller Myotomy**

A rare drawback of Heller myotomy without anti-reflux procedures is the development of diverticula at the myotomy site several years after surgery. In such patients, an inadequate decrease in LES pressure after myotomy
may lead to increased intraluminal pressure on the mucosa exposed by the myotomy at the anterior aspect of the esophagus. Dobashi et al. reported a giant epiphrenic diverticulum detected 20 years after an open Heller myotomy. The formation of this diverticulum was attributed to inadequate lowering of LES pressure, caused by an insufficient myotomy. Extension of the myotomy to 2 cm below the gastroesophageal junction is, therefore, essential to prevent the formation of diverticula after surgery. Even if an anti-reflux procedure is added to LHM, one study reported that esophageal diverticula developed in 7% of patients after LHM with Toupet fundoplication. Esophageal diverticula might be caused by exposure of the mucosa of the anterior aspect of the esophagus to the peritoneal cavity after myotomy by this procedure. In contrast, the incidence of diverticula is low after LHM with Dor fundoplication because the myotomy site is covered with a wrap.

**Thoracoscopic Heller Myotomy (THM)**

Thoracoscopic Heller myotomy (THM) results in excellent relief of dysphagia in the short term and is expected to have long-term outcomes similar to those of Heller myotomy done by open thoracotomy. On the other hand, anti-reflux procedures are often omitted when myotomy is performed under thoracoscopic guidance, increasing the risk of reflux esophagitis. Patti et al. reported a clinical study comparing the results of THM with those of LHM plus a partial fundoplication. Good or excellent relief of dysphagia was obtained in 90% of the study group as a whole (85% after THM and 93% after LHM). Gastroesophageal reflux developed in 60% of the patients after THM, as compared with 17% after LHM plus a partial fundoplication. Another drawback of THM was a longer postoperative recovery period as compared with laparoscopic surgery. A review article by Abir et al. reported that outcomes after THM were inferior to those after LHM. The inferior symptomatic outcomes after THM may be caused by difficulty in extending the myotomy adequately into the stomach from the chest and the inability to create a fundoplication.

**Subtotal Esophagectomy**

In patients who have a sigmoid esophagus associated with extremely severe dilation and curvature, dysphagia has been reported to persist after laparoscopic surgery without straightening the esophagus. In such patients, dysphagia may improve after subtotal esophagectomy. Esophagectomy should also be performed in patients with extensive dysplasia or carcinoma in situ of the esophagus. On the other hand, esophagectomy has several important drawbacks in patients with achalasia. It entails organ resection for a benign disease and has high rates of morbidity and mortality. Recently, minimally invasive subtotal esophagectomy has been successfully performed. As compared with LHM, minimally invasive esophagectomy offers similar symptomatic relief but requires a longer hospital stay. Because experience with minimally invasive esophagectomy remains limited, treatment outcomes, including long-term results, should be evaluated in well-designed clinical trials.

**Per Oral Endoscopic Myotomy (POEM) (Fig. 3)**

Per oral endoscopic myotomy (POEM) for the treatment of achalasia has recently been described by Inoue et al. This concept evolved from developments in natural orifice transluminal endoscopic surgery (NOTES). POEM is performed by creating a submucosal tunnel. An endoscopic myotomy of circular muscle bundles is then performed. The cut length is approximately 12 cm. Smooth passage of an endoscope through the gastroesophageal junction is confirmed at the end of procedure. Inoue et al. have treated 43 cases of achalasia, with a maximum follow-up period of 1 year 9 months. Symptoms of achalasia decreased or disappeared in all patients. The LES pressure decreased significantly after the procedure. No specific complications related to POEM were reported. Although about 10% of patients had gastroesophageal reflux disease after the procedure, symptoms resolved in response to treatment with a proton-pump inhibitor. POEM might not damage anti-reflux barriers such as phrenoesophageal ligamentous attachments and, therefore, may not additionally require an anti-reflux procedure. Gastroesophageal reflux is prevented to some extent.

In follow-up studies, Swanstrom et al. and von Renteln et al. used POEM to treat achalasia and reported similar, favorable results. Inoue et al. initially indicated POEM for the treatment of early-stage achalasia, but recently extended the indication range to all categories of achalasia, including sigmoid type. Although POEM is expected to become a state-of-the-art technique for minimally invasive surgery in patients with achalasia, it is associated with the risk of serious complications such as mediastinitis and peritonitis caused by perforation of the
esophagus or stomach. At present, therefore, POEM should be performed with caution and only by operators proficient in both esophagoscopic submucosal dissection and open or laparoscopic Heller myotomy. Wider use of POEM would require the results of large, multicenter clinical trials demonstrating the safety of this procedure. Follow-up studies should also be performed to establish the long-term effectiveness of POEM.

**Dilation vs. Surgical Therapy**

At present, PD and surgical procedures including Heller myotomy with fundoplication are the most effective treatment options for achalasia. Until recently, the only randomized controlled trial that compared outcomes after PD with those after surgical therapy in patients with achalasia was reported by Csendes et al.\(^{44}\) Outcomes were compared between dilation and open Heller-Dor myotomy after a median postoperative period of about 5 years in 81 patients with achalasia. The rate of improvement in passage disorders was higher in the open surgery group (95%) than in the dilation group (65%). However, an important limitation of this study was that dilation was performed with a Mosher bag rather than with a Rigiflex balloon dilator, currently considered the most effective dilator.

In 2007 Kostic et al. performed a randomized controlled trial that compared PD performed with a Rigiflex balloon dilator with LHM with Toupet fundoplication.\(^{45}\) The results showed that LHM with Toupet fundoplication was the superior procedure, but only 51 patients were studied, and follow-up was only 12 months.

In 2011 Boeckxstaens et al. reported the results of a randomized clinical trial comparing PD with surgical therapy. The overall study group was relatively large (201 patients).\(^{46}\) The surgical therapy group underwent LHM with Dor fundoplication, and the PD group underwent dilation with a Rigiflex balloon dilator, both of which are currently considered mainstays of treatment. The therapeutic success rate at 2 years was similar in the PD group and the LHM with Dor fundoplication group, and these procedures were concluded to be similarly effective. When a 35-mm balloon was used for dilation in this study, perforation occurred in 4 (31%) of 13 patients. The protocol was, therefore, amended during the study. When a balloon 30 mm in diameter was used for initial dilation, the perforation rate decreased to 4%. In either case, however, PD is associated with a substantial risk of perforation as a complication and has not been shown to be clearly superior to surgical therapy in terms of safety. Another limitation of PD is that its effect decreases with time, as mentioned above. Although follow-up was relatively long (mean, 43 months) in the study by Boeckxstaens et al., it remains unclear whether treatment effectiveness in the groups will remain similar after 5 to 10 years.

**PD vs. EBTI vs. Surgical Therapy**

Wang et al. performed a meta-analysis of randomized and controlled trials assessing treatment outcomes in patients with achalasia.\(^{47}\) The meta-analysis included 17 studies with 761 patients. The results indicated that the remission rate was higher for PD than for EBTI as initial intervention (relative risk [RR], 2.20; 95% confidence interval [CI], 1.51–3.20). As compared with PD, LHM further increased the remission rate (RR, 1.48; 95% CI, 1.48–1.87), and there was no difference in the rate of complications (RR, 1.48; 95% CI, 0.37–5.99). In another
study, Campos et al conducted a large systematic review and meta-analysis of 105 studies with 7855 patients.\textsuperscript{13)} The results indicated that symptom relief was better after PD than after EBTI (68.2% vs. 40.6%; odds ratio [OR], 3.4; 95% CI, 1.2-9.8; \( p = 0.02 \)), and the need for additional therapy was greater in patients who received EBTI (46.6% vs. 25%; OR, 2.6; 95% CI, 1.05–6.5; \( p = 0.04 \)). They reported that laparoscopic myotomy combined with an anti-reflux procedure provided better symptom relief (90%) as compared with all endoscopic and other surgical approaches, with a low rate of complications (6.3%).

**Conclusions**

As treatment for achalasia, the effectiveness of drug therapy is transient and limited. PD is superior to EBTI. The mainstay of surgical therapy is LHM with fundoplication. It is difficult to make definitive conclusions regarding the comparison between PD and LHM with fundoplication because accumulated evidence is lacking, but LHM with fundoplication appears to be the superior to PD at present. Although POEM is expected to become an effective state-of-the-art procedure for minimally invasive surgery, long-term outcomes and safety must be confirmed. The results of large randomized controlled trials with at least 5 years of follow-up are finally necessary to draw firm conclusions about the benefits and risks of each treatment option.

**Disclosure Statement**

None of the authors have any conflicts of interest to declare with respect to this study.

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