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EDITORIAL

Achalasia: A review of Western and Iranian experiences

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Abstract

Achalasia is a primary motor disorder of the esophagus, in which esophageal emptying is impaired. Diagnosis of achalasia is based on clinical findings. The diagnosis is confirmed by radiographic, endoscopic, and manometric evaluations. Several treatments for achalasia have been introduced. We searched the PubMed Database for original articles and meta-analyses about achalasia to summarize the current knowledge regarding this disease, with particular focus on different procedures that are used for treatment of achalasia. We also report the Iranian experience of treatment of this disease, since it could be considered as a model for medium-resource countries. Myotomy, particularly laparoscopic myotomy with fundoplication, is the most effective treatment for achalasia. Compared to other treatments, however, the initial cost of myotomy is usually higher and the recovery period is longer. When performing myotomy is not indicated or not possible, graded pneumatic dilation with slow rate of balloon inflation seems to be an effective and safe initial alternative. Injection of botulinum toxin into the lower esophageal sphincter before pneumatic dilation may increase remission rates. However, this needs to be confirmed in further studies. Due to lack of adequate information regarding the role of expandable stents in the treatment of achalasia, insertion of stents does not currently seem to be a recommended treatment. In summary, laparoscopic myotomy can be considered as the procedure of choice for treatment of achalasia. Graded pneumatic dilation is an effective alternative when the performance of myotomy is not possible for any reason.

INTRODUCTION

Achalasia is the most recognized primary motor disorder of the esophagus. In idiopathic achalasia, inhibitory ganglion cells in the myenteric plexuses of the esophagus undergo inflammatory degeneration. The term achalasia means "failure to relax"; the loss of ganglion cells leads to a defect in lower esophageal sphincter (LES) relaxation, which is the principal feature of idiopathic achalasia and causes functional obstruction of the esophagus, and reduced peristalsis in the esophageal body, which further impairs esophageal emptying. The functional obstruction in the LES is overcome only when the hydrostatic pressure of the retained material in the esophagus exceeds the LES pressure[1]. Secondary achalasia may occur following several conditions, which are listed in Table 1.

The reported annual incidence of achalasia is approximately 1 per 100 000[2]. Men and women are affected with equal frequency[3]. Although achalasia is diagnosed mainly in people aged between 25 and 60 years, it may occur at any age[2-4]. In general, achalasia has a subtle onset, and symptoms progress gradually. Therefore, patients experience symptoms for months or years before their disease is diagnosed. In a series of 87 patients with newly-diagnosed achalasia, the mean duration of symptoms was 4.7 years. The delay in diagnosis was due to misinterpretation of symptoms by physicians and atypical clinical manifestations[5]. Many patients are treated for other disorders such as gastro-esophageal reflux disease (GERD) before the diagnosis of achalasia is made[3]. The main symptom of achalasia is dysphagia[3]. To relieve dysphagia and other symptoms of achalasia, several treatments have been introduced,

including medical therapy, myotomy, pneumatic dilation of the LES, and injection of botulinum toxin into the LES. Early treatment of achalasia may also reduce the reported increased risk of esophageal cancer among patients with achalasia[6,7].

In this article, we report results of our review of medical literature on the subject of achalasia. Our aim is to summarize the current knowledge as regards this disease, with particular focus on different procedures that are used for treatment. Furthermore, several articles about achalasia have been published from Iran, mainly from the Digestive Diseases Research Center, Shariati Hospital of Tehran University of Medical Sciences, a nationwide referral center for the disease, where we provide follow-up care for 675 patients with achalasia. We present results of the Iranian studies, since our experience could be considered as a model for medium-resource countries.

PATHOPHYSIOLOGY

In achalasia, inhibitory ganglion cells in the myenteric plexuses of the esophagus, which produce nitric oxide, undergo inflammatory degeneration[8-10]. The remaining ganglion cells are often surrounded by lymphocytes and, to a lesser extent, by eosinophils[8,11]. Loss of inhibitory ganglion cells has two consequences: (i) basal LES pressure rises, which impairs normal relaxation of the sphincter and esophageal emptying, and (ii) the smooth muscle layer in the esophageal body loses normal peristalsis.

Several studies have suggested that a viral infection or some other environmental factor may initiate inflammation in the myenteric plexus. For example, a recent study suggested that the inflammatory reaction might be triggered by human herpes virus type 1[12]. In certain individuals, the inflammation may lead to an autoimmune response against ganglion cells. Genetic susceptibility may play a role in this process[13]. There are some reports of an association between some human leukocyte antigens and the presence of circulating antibodies to enteric neurons and the loss of ganglion cells[14]. An hereditary association between achalasia and some other conditions such as adrenal glucocorticoid deficiency and alacrima has been reported[15]. In our study on 25 children with achalasia, 2 cases (8%) had Achalasia, Alacrima, and Adrenal insufficiency (triple A syndrome or Allgrove syndrome) and 3 cases (12%) had Achalasia and Alacrima (double A syndrome). All of the 5 cases were siblings from two families[16].

CLINICAL FEATURES

The prevalence of the main symptoms of achalasia is shown in Table 2. The most common symptom of achalasia is dysphagia to solid foods (over 99%), followed by dysphagia to liquids (90% to 95%)[17]. Although dysphagia to liquids can occur in patients with other esophageal motility disorders (e.g. progressive systemic sclerosis), this symptom strongly suggests achalasia[3].

Regurgitation, active or passive, occurs in 70% to 80% of cases. Regurgitation can be troublesome; this may lead to aspiration when patients lie down[2,3]. Weight loss, chest pain, and heartburn occur in approximately 40% to 60% of patients. Although severe weight loss can happen, the usual weight loss is 5 to 10 kg.

Table 1 Causes of secondary achalasia

Malignancy, especially carcinoma
Chagas' disease
Amyloidosis
Sarcoidosis
Neurofibromatosis
Eosinophilic gastroenteritis
Multiple Endocrine Neoplasia, type 2B
Juvenile Sjögren's syndrome with achalasia and gastric hypersecretion
Chronic idiopathic intestinal pseudo-obstruction
Anderson-Fabry disease

Table 2 Prevalence of symptoms in achalasia

Symptom	Percentage (%)
Dysphagia to solids	99
Dysphagia to liquids	93
Active regurgitation	84
Passive regurgitation	68
Weight loss	61
Chest pain	59
Nocturnal cough	45
Heartburn	35
Nocturnal dyspnea	20
Hiccup	8

Occasionally, chest pain is the presenting symptom of achalasia. This is more common in younger patients, and tends to diminish with advancing age[17]. In our study of 213 achalasia patients, chest pain was the only symptom whose prevalence between the sexes was significantly different, being more common among women than men (70.9% *vs* 54.5%, $P = 0.03$, respectively)[18]. In both sexes, chest pain did not relate to the duration of symptom and the LES pressure. Chest pain was less frequently reported by patients over 56 years of age compared to those younger than 56 years ($P < 0.05$)[18]. It seems that chest pain is a distinctive symptom of achalasia which is affected by sex as well as age. Although chest pain was not improved following pneumatic dilation in some studies[17], others reported significant improvement after the procedure[18].

Heartburn occurs frequently in achalasia. Patients with heartburn have lower LES pressures than those without this symptom[19]. Heartburn may occur as a result of gastro-esophageal reflux or other causes, such as direct irritation of the esophageal mucosa by foods, pills, and the lactate produced by bacterial fermentation of retained carbohydrates[19,20]. Hiccup is also a frequent symptom in achalasia, partly because of the obstruction of the distal esophagus[21]. Functional and structural abnormalities of the lung, such as tracheo-bronchial compression and abnormalities on high-resolution CT-scan, may occur in half of the patients[22]. The frequency

Table 3 Frequency of cardinal symptoms in achalasia

Symptom	Frequency (%)			
	Each meal	Daily	Weekly	None
Dysphagia to solids	84	13	2	1
Dysphagia to liquids	60	25	8	7
Active regurgitation	33	36	15	16
	Daily	Weekly	Monthly	None
Passive regurgitation	20	44	4	32
Chest pain	12	39	8	41

of cardinal symptoms in achalasia is shown in Table 3.

Since patients with achalasia may experience retrosternal fullness following a meal, they may eat more slowly and induce regurgitation to relieve the feeling. They may perform some maneuvers to augment esophageal emptying, such as lifting the neck or throwing the shoulders back[3].

Compared to the general population, patients with achalasia are at substantially increased risk, even as high as 33-fold, of developing esophageal cancer. The cancer typically is of squamous cell type[6,7]. However, some series did not find any increase in the risk, particularly with early treatment of achalasia. We followed up 365 patients with achalasia for a mean duration of 43 mo; no case of esophageal cancer was identified. This may be related to the fact that our study participants were fairly young (mean age, 38 years) and the duration of follow-up was not very long[23].

DIAGNOSIS

Diagnosis of achalasia is based on clinical findings. The diagnosis is confirmed by radiographic, endoscopic, and manometric evaluations.

Radiography

The usual findings on a plain chest X-ray are widening of the mediastinum, due to esophageal dilation, and absence of the normal gastric air. When achalasia is suspected, barium swallow is the primary screening test. Barium swallow typically shows a dilated esophagus that terminates in a beak-like narrowing as a result of contraction in the LES. When dilation is very severe, the esophagus may have a sigmoid shape[3]. The overall sensitivity of barium swallow for diagnosis of achalasia is approximately 95%[24], but in early stages of the disease it may be reported as normal. For example, in a prospective study achalasia was suggested by barium examination in only 21 out of 33 patients who eventually were diagnosed with achalasia[2].

The timed barium esophagogram, which assesses esophageal emptying at 1, 3 and 5 min after swallowing of barium, can be more helpful than usual barium swallow. Vaezi *et al*[25] reported that assessing both symptom improvement and objective improvement in esophageal emptying can better identify the response rate to pneumatic dilation and need for repeated dilations in the future. In their study of 37 patients, there was a significant association ($P < 0.001$) between improvement in patient symptoms and barium height. In 38 out of 53 (72%) pneumatic dilations, the degree of symptom and barium height improvement was comparable. In 8 out of 26 (31%) patients, however, there was < 50% improvement in barium height despite near complete symptom resolution. Age was the only difference between the groups and patients with improvement in both symptoms and barium height, i.e. the first group, were significantly older than the second. They concluded that the timed barium esophagogram before and after dilation may identify a subset of patients with poor esophageal emptying but with good improvement in symptoms who may benefit from early repeated pneumatic dilation[25]. Similarly, Chuah *et al*[26] found in their study of 32 patients with achalasia who received pneumatic dilation that the timed barium esophagograms correlated with symptomatic improvement in up to 71% of patients, although seven patients who noted complete symptom resolution showed less than 50% improvement in barium column height and esophageal diameter. In a study of 52 patients, we also found that the volume of barium retention at 5 min could predict the LES pressure before and after balloon dilation in achalasia[27], and in a study of 43 patients, surface area of barium retention at 5 min appeared to be an even better predictor for resting LES pressure[28]. In a randomized clinical trial of 51 patients who underwent surgery or pneumatic dilation, results of the timed barium esophagogram also correlated well with outcome. Poor improvement in barium height following the treatments was associated with an increased risk of treatment failure[29].

Manometry

Manometry is the most sensitive tool for diagnosis of achalasia. Elevated resting LES pressure (usually > 45 mmHg), incomplete LES relaxation, and aperistalsis in the smooth muscle portion of the body of the esophagus are three characteristic manometric features of achalasia[30]. Swallows may be followed by either no esophageal contraction or simultaneous contractions. Simultaneous contractions may also occur spontaneously. Another common feature is that resting pressure in the body of the esophagus is slightly higher than in the stomach[3].

In most patients the amplitude of esophageal contractions is low. On the other hand, in vigorous achalasia the simultaneous esophageal contractions have high amplitudes (e.g. > 60 mmHg). Some studies have suggested that vigorous achalasia may represent an early form of achalasia in which some inhibitory ganglion cells may not yet be destroyed[8], and that patients with vigorous achalasia may benefit more from botulinum toxin injection than those with classic achalasia[31]. At present, however, the distinction between vigorous and classic achalasia seems to have little clinical significance.

Endoscopy

Endoscopy in achalasia typically reveals a dilated

esophagus that often contains retained material. The esophageal mucosa usually appears normal, although inflammation and ulceration may result from chronic inflammation caused by retained food or pills. Endoscopy may be reported as normal if it is carried out in the early stages of the disease or it is not performed by experienced endoscopists[2]. Achalasia at early stages may also be misdiagnosed as GERD. Food stasis and GERD are main factors contributing to esophageal mucosal inflammation in achalasia. The association between endoscopic food stasis and histological inflammation is significant, but endoscopic signs of esophagitis and histological inflammation are poorly associated. Because of low sensitivity of endoscopy to detect inflammation, surveillance endoscopy with biopsy sampling and assessment of stasis is warranted to detect early neoplastic changes[32]. The stasis may predispose the esophagus to *Candida* infection.

Although the LES in achalasia is contracted, the endoscope can usually be traversed easily into the stomach aided by gentle pressure on the scope[3].

Endoscopic ultrasonography (EUS) may show widening of the mean longitudinal and circular smooth muscle layers of the LES; however, this finding is not specific for achalasia[33]. We compared the esophageal muscularis propria thickness in achalasia patients with a control group using EUS and assessed the relationship between EUS findings and demographic features in both groups. The esophageal muscular layer was significantly thicker in patients with achalasia compared to control group ($P < 0.05$). Among patients with achalasia, the thickness at 5 and 10 cm above the gastro-esophageal junction appeared to be correlated with age, being higher among older people[34].

Clinical and endoscopic features of some other conditions, such as neoplasms, may be similar to those of achalasia. Since gastric adenocarcinoma is the most common neoplasm associated with pseudo-achalasia, the esophago-gastric junction and the gastric fundus should be carefully examined for any evidence of neoplasm. With certain features, malignancy is more likely: duration of symptoms less than 6 mo; presentation after the age of 60 years; excessive weight loss in spite of short duration of symptoms; difficult passage of the endoscope through the gastro-esophageal junction[35]. In these cases, repeated evaluations and biopsies are recommended.

Symptomatic scoring

Several scoring system have been proposed to evaluate the severity of the symptoms in achalasia. One of the scoring systems is shown in Table 4. In this scoring system, scores for the following five symptoms; dysphagia to solids, dysphagia to liquids, passive regurgitation, active regurgitation, and chest pain are summed up to calculate the total score. In a study of 116 patients with achalasia, we found a good correlation between this score and LES pressure ($r = 0.29$, $P < 0.01$)[36]. Among the main symptoms, active and passive regurgitation and dysphagia to liquids were significantly correlated to the LES relaxation pressure ($P = 0.001$, 0.002, and 0.046, respectively)[36].

Table 4 Scoring system for evaluation of clinical symptoms

Symptom	Score by frequency of symptoms			
	Each meal	Daily	Weekly	None
Dysphagia to solids	3	2	1	0
Dysphagia to liquids	3	2	1	0
Active regurgitation	3	2	1	0
	Daily	Weekly	Monthly	None
Passive regurgitation	3	2	1	0
Chest pain	3	2	1	0

TREATMENT

The mainstay of therapy is to reduce LES pressure in order to improve esophageal emptying by gravity. Several therapeutic modalities have been introduced to achieve this goal, including medical therapy, surgical myotomy (open or laparoscopic), pneumatic dilation of the LES, injection of botulinum toxin into the LES, and insertion of self-expanding stents. There are 3 recent meta-analyses of publications which have investigated different treatment approaches. One of these included 105 articles involving 7855 subjects, and investigated symptom relief, prevalence of gastro-esophageal reflux, and complications following treatments[37]. Pneumatic dilation was more successful in symptom relief than botulinum toxin injection (68% *vs* 41%, $P = 0.02$, respectively). Symptom relief with laparoscopic myotomy plus an anti-reflux procedure was better (90%) than with all other treatments. Furthermore, complication rate was low with this method (6.3%)[37]. Likewise, another meta-analysis of randomized and controlled treatment trials, which included 17 articles with 761 participants and investigated remission and relapse rates and complications, found a better remission rate and lower relapse rate for laparoscopic myotomy compared to other treatments. There was no difference between open and laparoscopic myotomy, in the only trial that compared these two methods, regarding remission and relapse rates. Remission rate following pneumatic dilation was higher than after botulinum toxin injection[38]. A meta-analysis of controlled and uncontrolled studies in the Chinese literature (43 articles with 1791 participants) also showed that myotomy was associated with higher initial and long-term remission rates than pneumatic dilation or botulinum toxin injection. Only 2 studies compared open myotomy with laparoscopic myotomy; there was no difference in remission rate[39]. Since results after any treatment may deteriorate over time, life-long follow-up and objective assessment of the results are recommended.

Medical therapy

Nitrates and calcium channel blockers (e.g. nifedipine) relax the smooth muscles of the LES[40]. These medications are usually taken sublingually 10 to 30 min before meals. Pharmacotherapy for achalasia, however, is often ineffective and frequently associated with side

effects (e.g. headache, hypotension, and tachyphylaxis). Therefore, nitrates and calcium channel blockers are primarily used for patients who are unwilling to undergo or unable to tolerate more effective, invasive forms of therapy[3].

Surgical myotomy

Surgical myotomy was first introduced by Ernst Heller in 1913. Nowadays, a modified technique is commonly used[41]. The standard "open" myotomy can be performed using either an abdominal or, more commonly, a thoracic approach[42,43]. More recently, laparoscopic and thoracoscopic techniques have been used to perform myotomy[39,44-46].

The modified Heller approach results in good to excellent relief of symptoms in 70% to 90% of patients with few serious complications. The mortality rate (approximately 0.3%) is similar to that reported for pneumatic dilation[42]. The major disadvantages of surgery are the high initial cost, long recovery period, and the frequent development of GERD. Reflux esophagitis develops in approximately 10% of patients treated by surgical myotomy[42]; however, the efficacy of proton pump inhibitor treatment minimizes its clinical significance. There is a debate with regard to the need for additional fundoplication in open myotomy. In some studies, gastro-esophageal reflux was relatively frequent even after combining myotomy with anti-reflux procedures[47,48].

There is increasing experience with Heller myotomy performed by minimally invasive techniques (laparoscopy or thoracoscopy), and these techniques have become the procedure of choice by many experienced surgeons for uncomplicated cases in Western countries. These approaches in several trials were more successful in symptom relief than other treatments[37]. They are associated with few major complications[49] and shorten the duration of hospitalization and recovery[44,45]. Some pre- and postoperative findings may be helpful in predicting the outcome. In a study of 407 patients who underwent laparoscopic myotomy, high preoperative LES pressure (> 30 mmHg) was a predictor of a good response, while severe chest pain and the presence of a decompensated sigmoid esophagus (class Ⅳ) was associated with poor outcome[50]. In a study of 200 patients who underwent laparoscopic or thoracoscopic myotomy plus a partial fundoplication, low LES pressure, presence of sigmoid esophagus, and longer duration of symptoms were associated with failure of treatment in long-term follow-up[51]. Preoperative LES pressure over 35 mmHg was also a strong predictor of excellent postoperative relief in dysphagia in another study of 200 patients[52].

Objective analyses have shown a high rate of gastro-esophageal reflux in laparoscopic myotomy without an anti-reflux procedure. In a study of 50 patients with achalasia who underwent laparoscopic Heller myotomy without anti-reflux procedures, significant heartburn was reported in 30% of cases. Twenty four-hour pH monitoring revealed abnormal findings in 11 out of 22 patients tested[53]. However, use of a fundoplication procedure with laparoscopic myotomy reduced the rate of gastro-esophageal reflux (8.8% with a fundoplication *vs* 31.5% without a fundoplication, $P = 0.003$)[37]. In a study of 20 patients who underwent laparoscopic myotomy and fundoplication, 24-h combined multichannel intra-luminal impedance and pH monitoring did not show any evidence of postoperative pathologic reflux in both upright and recumbent positions[54]. Few randomized trials have investigated the efficacy of different fundoplication techniques used with laparoscopic myotomy in treatment of achalasia. In a randomized, controlled study of 144 patients who underwent laparoscopic myotomy, the outcome when using Dor *versus* Nissen fundoplication was investigated. Both techniques were successful in long-term control of gastro-esophageal reflux, but the recurrence rate of dysphagia was higher with the Nissen method[55]. Based on the published literature, Dor fundoplication seems to be performed more commonly as the anti-reflux procedure during laparoscopic myotomy than other fundoplication techniques.

Pneumatic dilation

Although some studies reported similar short- and long-term efficacy for myotomy and pneumatic dilation, particularly with graded dilation (1-3 dilations with progressively larger balloons)[56,57], as mentioned earlier, myotomy has been shown to be a more effective treatment for achalasia in several trials[37,38]. However, pneumatic dilation is less expensive than myotomy and still improves symptoms in a substantial number of patients[58-60]. In a meta-analysis of uncontrolled studies, a single pneumatic dilation was found to be effective in 72% of patients during a mean follow-up of 4.9 years[61]. In a study of 150 patients with achalasia, pneumatic dilations were performed until remission was achieved or symptoms recurred, using an "on-demand strategy" based on symptom recurrence, and a long-term remission was achieved in nearly all patients[60]. Pneumatic dilation can also be applied for some patients in whom dysphagia persists after surgery[62,63]. In a study of 27 patients with recurrent dysphagia following surgery, pneumatic dilation improved symptoms in 76% of the patients[63]. If pneumatic dilation fails, laparoscopic myotomy with fundoplication can be performed; the outcome is not affected by previous pneumatic dilation[50,64].

A number of different balloon dilators have been used over the years. A systematic review of the treatment of achalasia compared the results of using different dilators; pneumatic dilation was performed in 2418 patients with "old" dilators, in 234 patients with the "new" Witzel dilator, and in 359 patients with the Rigiflex dilator[65]. Using old dilators and Witzel dilators, two-thirds of patients had good to excellent improvement after one or more dilations during a mean follow-up of 4.6 years and one year, respectively. Using Rigiflex dilators, an equivalent improvement was achieved in up to 90% of patients, depending upon the diameter of the dilator used (74% for 3.0 cm, 86% for 3.5 cm, and 90% for 4.0 cm)[65]. At present, the most popular pneumatic dilator is the Rigiflex balloon, which is passed over a guidewire and positioned

fluoroscopically or endoscopically in the LES. This balloon is available in three different sizes (3.0, 3.5, and 4.0 cm). The thinnest balloon is typically used in the first dilating session. The standard approach to balloon dilation is one dilatation per session; further need for dilation is based on the symptomatic response. Patients are usually referred to a surgeon if three consecutive dilations over a few months do not provide clinical remission. In long-term follow-ups, more than three sessions can be applied if symptoms recur.

In our center we perform all dilations with the Rigiflex balloon dilator. After a clear liquid diet for 24 h and an overnight fast, patients receive intravenous diazepam (5-10 mg) and meperidine (25-50 mg). A guidewire into the stomach is placed under endoscopic visualization. In the first dilating session, a 3.0 cm balloon dilator is passed over the guidewire under endoscopic guidance. The midpoint of the balloon is positioned at the LES. The balloon is gradually inflated to 6 pounds per square inch (psi) over 20 s and then to 8 psi for the next 20 s and finally to 10 psi for 60 s. Then the balloon is deflated and removed along with the guidewire. Patients are discharged after a 6-h observation period. If severe or sustained chest pain occurs, a gastrografin swallow is performed to rule out perforation.

Using the above method we conducted a study of 99 patients to assess therapeutic outcome after pneumatic dilation. Initially, all symptomatic patients underwent pneumatic dilation with a 3.0 cm balloon. If symptoms recurred, dilation was repeated with a 3.5 cm balloon. In the case of further relapse, a third dilation was carried out with a 4 cm balloon. The patients were followed for an average length of 47 (range, 18 to 60) mo. Dilation was repeated in 35 patients; only 6 of them required a third dilation. After the third dilation two patients did not display improvement and underwent myotomy. Over the study period, cumulative remission rate was 65% without re-dilation and 94% with re-dilation. The mean remission period was 44.7 mo[66].

To address the optimal method for performing pneumatic dilation, regarding the amount and rate of inflation pressure and balloon diameter, we conducted a large long-term prospective study and enrolled 262 achalasia patients over 10 years. In the first 62 patients (group A), dilation was done using a 3.5 cm balloon, which was inflated to the pressure of 10 psi over 10 s. In group B (200 patients), we initially used a 3.0 cm balloon with inflation pressure of 10 psi in 30 s. We used a Rigiflex balloon and maintained pressure for 60 s after inflation in both groups. If symptoms recurred, dilation was repeated with incrementally larger balloons (for second dilation, 4.0 cm in group A and 3.5 cm in group B; for third dilation, 4.0 cm in both groups). The cumulative proportional remission rates with single dilation after 6 mo were 83% and 75% in groups A and B, respectively; the corresponding rates decreased to 60% and 57%, respectively, after 30 mo. The difference between the 2 methods was not statistically significant. The remission rate following re-dilation was good; 1 year after the second dilation, it was 88% in group A and 89% in group B, and 2 years after the second dilation, it was 70% in both groups. All perforations ($n = 3$) occurred in group A at the first dilation (62 dilations) with rapid inflation of balloon (10 psi over 10 s); while there was no perforation in group B (296 dilations), in which gradual increasing of pressure (10 psi over 30 s) and graded dilation method was used[67].

In another Iranian study, 45 patients who underwent pneumatic dilation were compared with 19 patients who underwent open myotomy. Good to excellent relief was achieved in 68% of patients with myotomy and 80% of patients with pneumatic dilation. After over 2 years of follow-up, relapse rates in both groups were not significantly different (39% in surgery group and 25% in pneumatic dilation group). The mean length of hospital stay and days off from work were significantly lower in the pneumatic dilation group; these were discovered to be 9 and 39 d in the myotomy group and 1 and 2 d in the pneumatic dilation group, respectively[57].

Some predictors for the outcome of pneumatic dilation have been suggested, including age of patients[68,69] and a decrease in LES pressure following dilation[69]. In a study of 111 patients, short- and long-term remission rates were good (98% and 75% at months 24 and 60, respectively), but young age ($\leqslant$ 37.5 years), high esophageal body pressure, and high LES pressure ($\geqslant$ 17.5 mmHg) following first dilation were negative predictive factors. Young patients who required more than 2 dilations seemed not to benefit from this kind of treatment[70]. We did not find any significant association between age, gender, previous treatment, or severity of initial symptoms and the outcome of pneumatic dilation ($P > 0.4$)[66].

Esophageal perforation is the most important complication of pneumatic dilation. It occurs in approximately 3% to 5% of patients in most series, although the range varies from 0% to 21%[3,71]. Patients with esophageal perforation usually present in the first hours after dilation. A high index of suspicion should be maintained in patients complaining of sustained pain or discomfort after the procedure. Some patients respond to conservative treatment with antibiotics and parenteral nutrition but others need a surgical repair. Other complications of pneumatic dilation include development of intramural hematomas, esophageal mucosal tears, and diverticula at the gastric cardia[72]. Severe transient and intermittent post-procedural chest pain has been reported in approximately 15% of patients during the 24-48 h after dilation[73,74]. Although this symptom is disturbing, it is not harmful.

Botulinum toxin injection

Botulinum toxin is a potent inhibitor of acetylcholine release from nerve endings. The toxin theoretically relaxes the LES by decreasing unopposed cholinergic stimulation of the LES[75]. Although the effect of botulinum toxin injection generally is shorter than some other procedures, it can be useful under certain conditions. In patients with multiple medical problems who are poor candidates for more invasive procedures, as well as those unwilling to undergo either surgery or pneumatic dilation, botulinum toxin injection is the preferred approach. Older patients

and those who suffer from vigorous achalasia may benefit more from botulinum toxin[76]. A multicenter randomized study suggested that dose of botulinum toxin may be a predictor of outcome: the higher the dose, the better the response[77].

The use of botulinum toxin in achalasia was first introduced by Pasricha *et al*[78]. Several studies indicate that 65% to 90% of patients respond to a single injection within 1 mo. The effect of botulinum toxin lasts from 3 mo to more than one year[79-82]. Those who respond to the injection may do equally well after a second or even a third injection. In one series, for example, symptom relief was achieved in 75% of 57 patients who received repeated injections, as needed, during up to 2 years follow-up[31]. However, the effect decreases over time; some studies reported clinical remission rates of 50% and 30% at 6 and 12 mo, respectively, following botulinum injection[83]. Although a few studies reported that botulinum toxin injection could provide an efficacy equal to that of pneumatic dilation over a one year period[84], several randomized clinical trials have shown that while initial symptomatic remission rates by pneumatic dilation and botulinum injection may be similar in some cases, pneumatic dilation is associated with a significantly higher long-term remission rate[85,86]. In some studies, only pneumatic dilation was associated with improvement in objective measures of esophageal function, including esophageal manometry and barium studies[85,87]. In our trial of 40 patients, pneumatic dilation was more efficient than botulinum injection in providing sustained symptomatic relief over a 12 mo period. The remission rates for pneumatic dilation and botulinum injection after 12 mo were 52% and 15%, respectively[88].

Several formulations of botulinum toxin are available. A comparison between 100 U of Botox and 250 U of Dysport showed a similar efficacy for up to 6 mo of follow-up[89]. In the most common method for injection therapy, 1 mL aliquots (20 to 25 units/mL) of the toxin are injected into each of four quadrants, approximately 1 cm above the Z line, using a standard sclerotherapy needle. We use and recommend the following method. After an overnight fast, patients are sedated with intravenous diazepam (5-10 mg) and meperidine (25-50 mg). The LES is identified by visualization of the sphincter rosette at the squamo-columnar junction during upper gastrointestinal endoscopy. Four hundred units of Dysport are diluted in 4 mL normal saline. Two 50-unit aliquots (0.5 mL) of Dysport are injected through a 5 mm sclerotherapy needle into each quadrant of the LES. Patients are discharged when routine post-sedation care is completed and allowed to eat later on the same day. Improvement in symptoms is usually observed after only 24 h; peak effects occur even later in some patients.

Reported complications after botulinum toxin are not major and include post-procedural transient chest pain (25%) and heartburn (5%)[90]. Transient chest pain, the main complication, can be controlled by sedatives. Neutralizing antibodies have been detected in approximately 5% of patients treated chronically with botulinum toxin for skeletal muscle conditions; however, their significance in relapse of dysphagia in achalasia is uncertain. These antibodies, however, might be a possible cause of the rapid relapse of dysphagia following botulinum toxin injection[91]. Surgical treatment of achalasia in patients who previously received botulinum toxin may encounter some technical problems, but no significant difference in the outcome between patients with and without previous use of the toxin has been reported[92].

Pneumatic dilation after botulinum toxin injection

Only a few studies have investigated the effect of botulinum toxin injection on the outcome of pneumatic dilation. In a retrospective study of the effect of the combined therapy, we studied 12 patients who underwent dilation following botulinum toxin injection and 12 patients with achalasia who underwent only pneumatic dilation (control group). With combined therapy, only one of the patients relapsed 30 mo after dilation, while all the others were in remission for an average of 25.6 mo. In the control group, all the patients relapsed after a mean period of 12.6 mo and needed further dilation. The cumulative remission rate was significantly higher in the combined therapy group than in the control group ($P < 0.01$). One month after dilation, the mean symptom score decreased by 76% in the combined therapy group and by 53% in the control group. Age, sex, duration and severity of symptoms were not correlated with response to treatment[93].

We also conducted a prospective trial. Twenty seven patients were randomly assigned to receive botulinum toxin 1 mo before pneumatic dilation and 27 patients were assigned to undergo pneumatic dilation alone. One-year remission rates of patients in the botulinum toxin-pneumatic dilation group and the pneumatic dilation group were 77% and 62%, respectively ($P = 0.1$). In the pneumatic dilation group, the esophageal barium height significantly decreased at 1 mo ($P < 0.001$), but this reduction did not persist over 1-year follow-up. The botulinum toxin-pneumatic dilation group showed a significant reduction in barium height at both 1 mo and 1 year after treatment ($P < 0.001$). In the botulinum toxin-pneumatic dilation group, 91% of patients older than 40 years were in remission at 1 year, compared with only 55% of this age group in the pneumatic dilation group ($P = 0.07$)[94].

We found an abstract in English that reported a series of 9 patients with achalasia who were treated with application of 250 IU Dysport into the LES and balloon dilation 7 d later. Two patients underwent myotomy because of poor relief of symptoms. Seven other patients, however, were in good symptomatic remission after one year. The remission was even observed for as long as 36 mo, which was the longest follow-up period[95].

Insertion of stents

Only a few studies have investigated the role of expandable stents in treatment of achalasia[96-99]. The results are controversial. Therefore, insertion of stents does not seem to be a currently recommended treatment for achalasia.

CONCLUSION

First stages of achalasia may be misdiagnosed as other diseases, such as GERD. Myotomy, particularly laparoscopic myotomy with fundoplication, is the most effective treatment for achalasia and can be considered as the procedure of choice. Compared to other treatments, however, the initial cost of myotomy is usually higher and the recovery period, particularly following open myotomy, is generally longer. When performing myotomy is not possible for any reason, e.g. medical contraindication, patient's unwillingness, when patients cannot afford surgery, or experienced centers for surgery or post-operative care are not easily accessible (situations that may not be rare particularly in some low- or medium-resource countries), graded pneumatic dilation (using 3.0 cm balloons initially) with slow rate of balloon inflation seems to be an effective and safe initial alternative. The duration of remission can be extended by repeated dilation with larger-sized balloons. Injection of botulinum toxin into the LES before pneumatic dilation seems to increase remission rates. However, this needs to be confirmed in further studies. The timed esophagogram may be used as a non-invasive objective tool for initial and post-operative or post-dilation assessment.

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