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EDITORIAL

Non-surgical treatment of esophageal achalasia

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Abstract

Esophageal achalasia is an infrequent motility disorder characterized by a progressive stasis and dilation of the oesophagus; with subsequent risk of aspiration, weight loss, and malnutrition. Although the treatment of achalasia has been traditionally based on a surgical approach, especially with the introduction of laparoscopic techniques, there is still some space for a medical approach. The present article reviews the non-surgical therapeutic options for achalasia.

Key words: Achalasia; Botulinum toxin; Pneumatic dilatation

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INTRODUCTION

Esophageal achalasia is a rare neuromuscular disorder characterized by degenerative changes of myenteric plexus leading to a selective loss of inhibitory nerve endings. The consequences of this damage are the irreversible loss of peristaltic contractions and the impaired relaxation of the lower esophageal sphincter (LES)[1]. The ultimate cause of ganglion cell degeneration is unknown, but an association with class Ⅱ HLA antigens[2,3] and some virus infections[4,5] has been described. An autoimmune pathogenesis in achalasia has been hypothesized due to the description of antimyenteric neuron antibodies in a subset of patients[6], although a genetic predisposition cannot be excluded[7,8].

If untreated, in due course the disorder causes a progressive stasis and dilation of the oesophagus; with subsequent risk of aspiration, weight loss, and malnutrition. Because the etiology of achalasia remains obscure, the treatment is strictly palliative and is aimed at reducing the basal and residual LES pressure. Thus, esophageal emptying is allowed by gravity. The treatment of achalasia has traditionally relied on a surgical approach; the advent of minimally invasive surgery with a shorter hospital stay, reduced morbidity, and quicker return to daily activity, makes this option even more attractive[9,10]. However, the high cost of this approach, the access to reference centers, the surgeon's learning curve, and some methodological debates, are still an issue.

In contrast, there is presently recent evidence that some medical strategies may be of benefit in many patients with this disorder[11-13]. This review summarizes the current knowledge of non-surgical management of achalasia.

PHARMACOLOGIC TREATMENT

A number of pharmacological agents have been used to decrease the LES pressure. However, most acute and chronic studies were uncontrolled ones, and usually included only a small number of patients. Very few single- or double-blind, placebo-controlled trials are available. Overall, the clinical efficacy is often poorly described, even though several studies have shown that some compounds may be temporarily useful, while waiting for a more definitive therapeutic option. Table 1, Table 2, and Table 3, report the results of the most acute, chronic, and controlled studies, respectively.

The nitrates are claimed to be effective in achalasia; however, the relatively high frequency of side effects and the lack of controlled studies limits their clinical use[14]. Therefore, the calcium channel blockers have been more frequently used. In particular, nifedipine has the wider published clinical and experimental evidence of efficacy. The therapeutic schedule suggests a sublingual administration of 10-20 mg, 15-30 min before meals. Its efficacy varies largely (between 50% and 90% in clinical trials), with side effects complained by up to 30% of patients. These include peripheral edema, headache and hypotension, and may wane over time. To date, however, nitrates and nifedipine could be recommended only in patients with an early stage disease, as a temporary measure before a more definitive option is selected.

Table 1 Acute drug studies in esophageal achalasia

Author	Drug	*n*	% of LES decrease
Wright (1961)	Butylschopolamine	3	Decreased
Von Weiser (1977)	Nifedipine	6	30
Becker (1981)	Verapamil	3	Unchanged
Cargill (1982)	Nifedipine	6	Decreased
Hongo (1982)	Nifedipine	8	45
Di Marino (1982)	Carbutoerol	10	55
Nashrallah (1983)	Nifedipine	7	55
Becker (1983)	Verapamil	7	31
Traube (1984)	Nifedipine	20	30
Wong (1987)	Terbutaline Aminophyllin	15	Decreased
Bassotti (1988)	Nitroglycerin	9	70
Guelrud (1992)	VIP	6	51
Marzio (1994)	Cimetropium	20	Decreased
Penagini (1994)	Loperamide	9	Decreased
Bortolotti (1994)	Isosorbide	9	49
	Nifedipine	7	65
Bortolotti (2000)	Sildenafil	7	50

Table 2 Chronic drug studies in esophageal achalasia

Author	Drug	*n*	% efficacy	Follow-up (mo)
Yon (1975)	Anticholinergics	7	14	12
Gelfond (1981)	Isosorbide	24	79	2-19
Silverstein (1982)	Diltiazem	8	50	6
Gelfond (1982)	Nifedipine	15	53	8-14
Traube (1983)	Nifedipine	14	65-80	6
Maksimak (1986)	Nifedipine	4	LES decrease	3-6
Garia (1987)	Nifedipine	20	LES decrease	4
Coccia (1992)	Nifedipine	14	77	21

Table 3 Controlled drug studies in esophageal achalasia (NA = not available)

Author	Drug	*n*	% efficacy	LES decrease	Follow-up (mo)
Lobis (1976)	Dicyclomine	10	NA	42%	Acute
Bortolotti (1981)	Nifedipine	20	90	40%	6-18
Nashrallah (1985)	Nifedipine	4	75	Unchanged	1
Traube (1989)	Nifedipine	10	NA	28%	1
Triadafilopoulos (1991)	Nifedipine	14	NA	Decreased	1
	Verapamil	14	NA	Decreased	1

Table 4 Effect of BoTx on esophageal achalasia (only studies with at least 30 patients are reported)

Authors	Toxin units	*n*	% LES decrease	Response 1 mo (%)	Response 6 mo (%)	Response 12 mo (%)
Pasricha, 1996	80	31	45	90	55	-
Fishman, 1996	100	60	-	88	-	46
Cuilliere, 1997	80	56	31	75	60	-
Annese, 1998	100	57	55	88	55	35
Prakash, 1999	80	42	-	90	64	41
Kolbasnik, 1999	100	30	28	77	37	29
Annese, 1999	100-250	78	42	86	61	-
Annese, 2000	Variable	118	34	82	53	-
D'Onofrio, 2002	100	37	-	84	-	67
Storr, 2002	100	40	-	-	68	-
Martinek, 2003	100-250	49	65	93	-	41
Zaninotto, 2004	100	40	-	-	66	34

BOTULINUM TOXIN TREATMENT

Botulinum neurotoxins (represented by seven serotypes, abbreviated BoTx A to G) cause a sustained inhibition of neurotransmitter release at cholinergic terminals. These toxins specifically bind the presynaptic membrane, and enter the cytosol of the nerve terminal where they cleave different proteins involved in neuroexocytosis. The botulinum toxin A, which is currently used for the treatment of various dystonic skeletal muscle disorders, cleaves the SNAP-25 molecule at the presynaptic membrane, thus blocking the acetylcholine release and causing a denervation atrophy. Its beneficial effects are currently being extended to a variety of diseases with increased cholinergic function[15-17].

The above considerations prompted Pasricha and colleagues to evaluate, for the first time, the usefulness of intrasphincteric injection of BoTx in esophageal achalasia[18,19]. The rationals was that the selective loss of the inhibitory nerves in achalasia upsets the excitatory (cholinergic) influences on LES. Thus, by blocking the release of acetylcholine, locally injected BoTx might reduce the LES pressure and improve the "passive" esophageal emptying. These authors developed a protocol that has become, with slight modification mostly due to the different toxin dosages, the standard one currently used in almost all centers. The toxin is injected through a standard sclerotherapy needle during an upper endoscopy performed under conscious sedation, and 80 to 100 Units of BoTx A are injected in each quadrant of the LES at 4 to 8 sites in 1 or 0.5 mL aliquots. Following the first observation, several investigators have found a success rate of 70% to 100% in relieving symptoms in the short-term with a parallel decrease of LES pressure and improvement of esophageal emptying, although probably to a lesser extent than that obtained after pneumatic dilation.

Table 4 summarizes most of the largest studies published on BoTx in achalasia; after a single injection of toxin, almost 80% of patients report good to excellent relief of symptoms. More than half are still in remission at six months and one third at one year. This waning of efficacy was expected on the basis of neurological experience[20]. The presynaptic nerve endings of skeletal muscles start to sprout new branches after 2-3 mo thus re-innervating the neuromuscular junction; for this reason, in a neurological setting, the injection of toxin is repeated every 3-4 mo. The effect of toxin on gastrointestinal smooth muscle and myenteric plexus has yet to be elucidated; nevertheless, the mean duration of a single injection of toxin in esophageal achalasia is 10-12 mo, with a wide variability ranging from three months up to three years. The reason for such variability is unknown,

but is probably related to another drawback of the toxin: the development of an autoimmune response with the production of antibodies that may in turn decrease its efficacy in some patients. This problem, however, could be solved with the use of different serotypes (i.e. BoTx C) which bind to different presynaptic receptors[21].

In the attempt to optimize the dose and time of administration of toxin, two multicenter studies, coordinated by our centers, have been recently performed. The first trial[22] demonstrated the relative similarity in the efficacy of 100 Units of Botox® (Allergan) with 250 Units of Dysport® (Ipsen, U.K.), the other commercially available toxin A in our country. Another study found the advantage of early repetition of the toxin with a second injection of 100 Units after one month[23]. This schedule allowed a remission rate of 75% at one year compared with a 35% rate obtained with the same amount (200 Units) in a single injection. Interestingly, this schedule has been proven to be effective in older (or aging) (more than 75 years) achalasic patients in inducing symptom remission[24].

Only a few studies are available on the long-term efficacy of BoTx. Pasricha *et al*[25] reported a 30% efficacy rate after a mean follow-up of more than two years, despite repeated injections. In our experience, however, 72% of patients were still in remission after a mean follow-up of 18 mo, provided that the toxin was repeated when symptoms relapsed[26]. More recently, after a mean follow-up of 49 mo (range 6-100 mo), we found a 70% rate of good or excellent control of symptoms in a series of 149 patients (Annese V, *et al,* unpublished data).

Overall, the endoscopic injection of toxin has been remarkably safe, and this is a common experience with this approach[27]. In less than 10% of patients, a mild chest pain develops shortly after the procedure, but this usually does not require specific treatment. More importantly, in case of failure, the injection of toxin does not influence the functional results of subsequent surgical myotomy or dilatation. However, a number of surgeons have reported, similarly to the situation found after repeated dilations, a more difficult myotomy because of an increased adhesion of muscular layers to mucosal plan with an increased danger of mucosal perforation during the procedure. However, no need of conversion to open approach has been reported in these patients.

PNEUMATIC DILATATION

Historically, the dilation was the first attempt of therapy in esophaegal achalasia, described in 1674 by Sir Thomas Willis[28]. In that case (and in subsequent ones) a whale bone with a sponge tip was successfully used, at least in the short-term. Later, mercury-filled bougies and metal devices were used. More modern dilators consisted of expanding bags or balloons that dilated forcefully the LES, rupturing muscular fibers, like the Syppy pneumatic dilator. The dilators more commonly used today are the polyethylene Microvasive Rigiflex dilator (Boston Scientific Co.), passed over a guided wire, and the Witzel dilator (American Endoscopy) consisting of a polyurethane balloon, mounted over the endoscope.

Forceful dilation of the LES is considered to date to be the most effective non-surgical treatment for achalasia, although details of the procedure vary in different institutions. The main variables are the type of dilator used, fluoroscopic or endoscopic positioning, and the degree and duration of inflation. We prefer to carry out the procedure under fluoroscopic control in a supine position, as previously described[29]. Nothing is allowed by mouth for at least 8 h before the procedure. Intravenous midazolam is used for conscious sedation. The dilator is passed over a guidewire, placed endoscopically in the stomach, and positioned across the diaphragmatic hiatus using radiopaque markers as guides. The correct location is assessed by moving the balloon until the waist at inflation of 2-3 psi is observed fluoroscopically in the midportion of the balloon. We start with a 30-mm diameter balloon in the first session; the balloon is inflated to 5 psi during 1 min and subsequently (depending on patient tolerance) to 10-12 psi, and pressure is maintained for another minute. If the procedure is well tolerated, a second session is performed in the consecutive day with a 35-mm balloon, once again in two steps at 5 and 10-12 psi, until the obliteration of the waist occurs. If no symptoms develop during the following 6 h, patients are allowed to eat. If symptoms (fever, chest pain, or cough) or abnormality at chest auscultation occur, a gastrografin swallow is performed. When mucosal tears are observed at the predilation endoscopy, the dilation is postponed for a month.

Overall, a literature analysis of more than 3000 patients showed that the efficacy of pneumatic dilation is 85% in relieving symptoms, with a range of 65%-90%. The average decrease in LES pressure is 54% (range 40%-65%) (V. Annese and G. Bassotti, unpublished data). The results obtained with Rigiflex dilators closely approach those obtained with myotomy, with a perforation rate of about 2%. This is probably the main drawback of pneumatic dilation, which often may require a surgical repair. Risk factors are the use of a large size balloon, and previous dilations. Another drawback of pneumatic dilation is a possible relapse of symptoms, which require additional dilations. This figure is still puzzling, due to large variability between studies and the scanty long-term reports; however, 20%-50% of patients may require additional dilations.

CONCLUSIONS

Achalasia is still an intriguing "mystery", and although different "solutions" are available the definitive "cure" is missing. The variety of therapeutic options may confound patients and doctors; therefore, controlled trials are welcome. These studies, besides the relief of symptoms, should also give information on esophageal emptying, long-term efficacy, patients' satisfaction, cost of procedure, availability of access to referral centers. Unfortunately, it has been estimated that to reach an adequate statistical power a large size trial should be realized, with more than 400 patients enrolled. Waiting for this information, the patients should be informed about all the therapeutic options and institutional experience.

In young patients (under 40 years) or in the presence of a large diameter (> 5-6 cm) oesophagus, a laparoscopic

myotomy is probably the better choice. In the group of patients between 40 and 65 years of age, the graded pneumatic dilation using the Rigiflex balloon should be advised. In elderly patients, poor candidates for surgery, and probably in patients with vigorous achalasia, the initial treatment with botulinum toxin should be the preferred approach. The toxin is also helpful when the pneumatic dilation or myotomy failed[30] or as a temporary measure.

The usefulness of nifedipine and nitrates is scarce, and these drugs should be used only on a temporary basis, waiting for more effective therapeutic options. In contrast, this pharmacologic approach may be useful on demand in case of severe chest pain.

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