

# Review article: the management of achalasia – a comparison of different treatment modalities<sup>1</sup>

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## SUMMARY

### Background

Achalasia is an uncommon primary oesophageal motor disorder with an unknown aetiology. Therapeutic options for achalasia are aimed at decreasing the lower oesophageal sphincter pressure, improving the oesophageal emptying, and most importantly, relieving the symptoms of achalasia. Modalities for treatment include pharmacologic, endoscopic, pneumatic dilatation and surgical. The decision of which modality to use involves the consideration of multiple clinical and economic factors.

### Aim

To review the management strategies currently available for achalasia.

### Methods

A Medline search identified the original articles and reviews the published in the English language literature between 1966 and 2006.

### Results

The results reveal that pharmacotherapy, injection of botulinum toxin, pneumatic dilatation and minimally invasive surgical oesophagomyotomy are variably effective at controlling the symptoms of achalasia but that each modality has specific strengths and weaknesses which make them each suitable in certain populations. Overall, pharmacologic therapy results in the shortest lived, least durable response followed by botulinum toxin injection, pneumatic dilatation and surgery, respectively.

### Conclusion

The optimal treatment for achalasia remains an area of controversy given our lack of complete understanding about the pathophysiology of the disease as well as the high numbers of clinical relapse after treatment. Further research focusing on optimal dosing of botulinum toxin injection and optimal timing of repeated graduated pneumatic dilations could add to our knowledge regarding long-term therapy.

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## INTRODUCTION

Achalasia is an oesophageal disorder characterized by the complete absence of oesophageal peristalsis and incomplete relaxation of the lower oesophageal sphincter (LES). The primary aetiology of achalasia remains unknown but the pathophysiology results in the loss of inhibitory neurons in the oesophageal myenteric plexus.<sup>1</sup> Despite being a rare disorder, affecting one per 100 000 subjects, achalasia can cause significant symptoms including dysphagia, chest pain, regurgitation and heartburn.<sup>2</sup> As the underlying pathogenesis of achalasia cannot be reversed, management strategies are focused on reducing the LES pressure. Decreasing the LES pressure facilitates emptying of the oesophageal content by gravity and thus reduces the associated symptoms. The treatment options that are currently used for achalasia are aimed at palliation of symptoms and improvement in oesophageal emptying. Options for therapy currently include pharmacologic, endoscopic, pneumatic dilatation and surgical modalities. These management options will be reviewed in this article with an emphasis on prospective and comparison data.

## METHODS

Using Medline, we identified the English-language original journal articles and reviews published between 1966 and May 2006. Search terms initially included 'achalasia' and 'treatment' with limits to 'clinical trials', 'English language' and 'adults'. The references of pertinent articles were reviewed and relevant manuscripts were included for review. Emphasis was placed on the data from randomized, prospective studies when available.

## PHARMACOLOGIC THERAPY

The use of pharmacologic therapy for the treatment of achalasia, if effective, would be preferable over the more invasive options for treatment. Unfortunately, such treatment is not focused at eliminating the underlying disease process but only temporarily improves the conditions that lead to symptoms. Calcium channel blockers and nitrates taken 30–60 min before meals have traditionally been the focus of pharmacologic therapy. Calcium channel blockers inhibit cellular uptake of calcium and as intracellular calcium

is necessary for contraction, relaxation occurs. Nitrate therapy acts by compensating for the decrease in the inhibitory neurotransmitter nitric oxide. This allows for a decrease in the chronic LES tone and a subsequent decrease in LES pressure. Both sublingual isosorbide dinitrate and nifedipine have been shown to decrease the basal LES pressure<sup>3–5</sup> although the effect of isosorbide dinitrate has both a faster onset and is more intense than that of nifedipine.<sup>4</sup> Additionally, isosorbide dinitrate has been shown to improve oesophageal emptying.<sup>3</sup> Both medications have variable results in alleviating the symptoms associated with achalasia<sup>3,5</sup> with initial improvement rates ranging from 50% to 90%.<sup>6</sup> Unfortunately, use of these medications long-term often promotes tolerance which severely diminishes effects over time.<sup>7</sup> Significantly, however, nifedipine has been shown to induce the long-term remission and even normalization of physiology in a minority of patients.<sup>7</sup> Verapamil has been shown to decrease the LES pressure, but did not demonstrate symptomatic improvement.<sup>8</sup> Unfortunately, the common side effects of hypotension, headache and peripheral oedema occur in about 30% of patients taking the sublingual calcium channel blockers or nitrates and this limits their clinical use. The side effects are more profound with nitrates<sup>3</sup> and thus calcium channel blockers are used more commonly.

Sildenafil has been proposed as an alternative pharmacologic agent for the treatment of achalasia given its inhibitory effects on phosphodiesterase type 5, which prevents the destruction of nitric oxide-stimulated cyclic guanosine monophosphate. This action causes an inhibitory effect on the smooth muscle and preliminary data demonstrate its ability to decrease the LES tone and residual pressure.<sup>9</sup> Further studies need to be done to determine whether this is of clinical utility in achalasia. Additionally, terbutaline sulphate and aminophylline have been shown to decrease the LES pressure. Oesophageal emptying, however, improved with terbutaline but not with aminophylline.<sup>10</sup> The clinical utility of these medications has not been further demonstrated.

Overall, while most patients with achalasia require endoscopic therapy, pneumatic dilatation, or surgical management, careful selection of patients for use of pharmacologic therapy may yield acceptable results. Pharmacologic therapies may be used successfully as a 'bridge' to more definitive therapy or in those in whom other treatments are contraindicated.

## ENDOSCOPIC THERAPY

The primary modality of endoscopic therapy in the treatment of achalasia is the injection of botulinum toxin into the LES. Botulinum toxin is a potent inhibitor of the release of acetylcholine, which serves as an excitatory influence of LES tone. Injection of botulinum toxin into the LES has been shown to improve the symptoms (dysphagia, regurgitation, and chest pain), decrease the LES pressure, improve the oesophageal emptying, and increase the LES aperture when compared with injection of placebo.<sup>11, 12</sup>

Multiple prospective trials have repeatedly demonstrated short-term benefits from botulinum toxin injections (Table 1). Unfortunately, single doses of botulinum toxin have clinical effects that are short in duration with relapses that are usually >50% within several months. Typically 80–100 U of botulinum toxin is injected in divided doses in a four-quadrant manner into the LES. There is a wide variability of practice concerning repeating sessions of botulinum toxin injection and the timing of these subsequent sessions. These differences in the dosing regimens appear to be clinically significant and may explain some of the variability in success between studies. The optimal dose regimen remains unknown but a large randomized study demonstrated that a 100-U injection followed by repeat injection in 1 month in initial responders had a significantly longer symptom-free time and a lower rate of symptom recurrence (19%) than other dosing regimens over a mean of

13 months.<sup>13</sup> The longer-term durability and the duration of response of botulinum toxin therapy continue to be a subject of scrutiny in patients treated with botulinum toxin injection but repeated injections may confer clinical benefit in 60–85% at 2 years.<sup>13–17</sup> Recent comprehensive data reported from the Cleveland Clinic demonstrated that 21% of newly diagnosed achalasia patients were treated with botulinum toxin as the initial modality of treatment from 1994 to 2002. The mean number of sessions required was two and the average duration of the effect was 6 months. Forty-three per cent of these patients required treatment with another modality to control symptoms.<sup>18</sup>

It does not appear to make a clinical difference which manufacturer produces the botulinum toxin<sup>19</sup> and there is evidence to support the possibility that antegrade (from the oesophagus) and retrograde (from a retroflexed view from the stomach) injection may provide a superior clinical effect.<sup>20</sup> It remains unclear whether the use of botulinum toxin injection for achalasia can cause the development of antibodies directed at the botulinum toxin that would decrease the therapeutic effect of this therapy.

Various studies have attempted to establish the predictors of response for botulinum toxin. The data thus far support the following positive predictors: age >50 years, the presence of vigorous achalasia, an initial clinical response to botulinum toxin, and a decrease in LES pressure in response to botulinum toxin.<sup>13, 15, 16, 22, 23, 25</sup>

Table 1. Prospective studies of botulinum toxin in achalasia

Ref. no.	No. patients	Dose (U)	No. treatment sessions	Decrease in LES pressure (%)	Immediate remission (%)	~6-month remission (%)	~12-month remission (%)	~24-month remission (%)
21	10	80	1	44	90		60	
11	21	80	1	33	82	67		
22	31	80	1–2		90	65	44	
23	60	80–100	1		70		36	
24	16	80	1–2		75	43		
25	55	80	1	30	72	63		
14	20	100	1–5		80			75
15	30	80	1–3		77		65	60
13	40	50	1–2	33	75			29
		100	1–2	31	84			68
		200	1–2	34	88			27
	118				82			
16	37	100	1–2	30	84		84	84

Injection of botulinum toxin appears to be a safe modality. Specific contraindications are few and include hypersensitivity to albumin, a previous reaction to injections of botulinum toxin and pregnancy. There is a small incidence of self-limited chest or epigastric pain, which does not appear to be dose-dependant. The treatment with botulinum toxin injection may have a beneficial effect on subsequent pneumatic dilatations and initial data report that response to subsequent dilatations may be enhanced by prior injection with botulinum toxin.<sup>26</sup> The consequence of prior injections of botulinum toxin in patients that subsequently require surgical therapy remains controversial.<sup>27, 28</sup> Additionally, botulinum toxin has been used in patients in whom the surgical myotomy or pneumatic dilatation is unsuccessful.<sup>22, 24 29-31</sup>

In addition to botulinum toxin injection, there is limited data on the use of polidocanol and ethanolamine injections into the LES. Further research needs to be conducted to determine if these therapeutic modalities hold any promise.<sup>32, 33</sup>

Overall, botulinum toxin is part of the gastroenterologist's armamentarium to treat achalasia. Given the data, it may be a reasonable initial therapeutic option in patients diagnosed with achalasia as it does not appear to preclude more invasive treatments at a later time. Additionally, it may be the primary therapy in those that are not candidates for pneumatic dilatation or surgery given its safety profile. When used, a second treatment of 100 U at 1 month should strongly be considered in patients who responded to the initial therapy.

## PNEUMATIC DILATATION

Pneumatic dilatation of the LES has been shown to be an effective modality for treating the achalasia. The proposed advantage of pneumatic dilatation is that it achieves symptomatic relief while being able to avoid the risks associated with more invasive surgery. The risk of perforation, however, has limited some from performing pneumatic dilatations.

Pneumatic dilatations have been performed on an out-patient basis for several years with initial success rates of 95%.<sup>34</sup> The Rigiflex (Microvasive) balloon dilator is the most commonly used dilator and has been demonstrated to be effective. Early data included 24 patients treated initially with a 30-mm Rigiflex balloon dilatation and showed resolution of symptoms in 70% and a 60% decrease in LES pressure. Subsequent

dilatation with a 35-mm Rigiflex balloon had a clinical response rate of 93% and a decrease in LES pressure of 68%.<sup>35</sup> Similar results have been reported subsequently and many dilate safely using a graduated approach up to 40 mm with a 93% response.<sup>36, 37</sup> A review by Vaezi and Richter demonstrated a cumulative success rate at a mean of 2 years of 74%, 86%, and 90% for the 30-, 35- and 40-mm dilators, respectively.<sup>38</sup>

Recent long-term data seem to support the possibility of durable results with low complication rates using a graduated dilatation approach.<sup>39</sup> Data from a study of 50 patients showed that 80% required a single dilatation for symptomatic improvement while the remainder required up to three serial dilatations. One-year follow-up revealed an 83% response rate. Long-term follow-up ranging from 2 to 7 years revealed a response of 67%. Similar data of 150 patients using pneumatic dilatation as initial therapy and with subsequent dilatations for recurrent dysphagia demonstrated a 96% remission rate over a mean of 45 months.<sup>40</sup> Additionally, it has been shown that LES pressure remains significantly lower at 1 and 5 years after dilatation.<sup>41</sup> Retrospective data from the Cleveland Clinic demonstrated that 41% of the untreated achalasia patients underwent pneumatic dilatation as their primary modality of therapy. The maximum dilatation required for relief of symptoms was 30 mm in 55%, 35 mm in 35% and 40 mm in 10%. The symptomatic response was seen in 86% of patients and improved oesophageal emptying was noted in 54% of patients. In addition, there was a good response when pneumatic dilatation was used after other modalities (botulinum toxin injection or surgical myotomy) were unsuccessful. Conversely, 19% of patients getting pneumatic dilatation as their initial modality of treatment required other subsequent modalities of treatment (surgical myotomy most commonly).<sup>18</sup>

Varying techniques for pneumatic dilatation have been studied. Data have demonstrated that a shorter duration of balloon inflation as well as use of conservative dilator sizes may be equally efficacious as more aggressive initial dilatations.<sup>42-44</sup> In addition, there have been various other dilator types besides the Microvasive Rigiflex that have been evaluated with the Witzel dilator being the second most common.<sup>45-49</sup> Metal stents have also been described as a means of temporary dilators of the LES.<sup>50</sup> Unfortunately, there is little standardization with these other methods.

In addition to the data above, other large series have shown low rates of oesophageal perforation when dilatations are done by experienced gastroenterologists. Multiple large series and reviews show a perforation rate of <1–3%.<sup>18, 38, 51–53</sup> It has been noted that the risk of perforation is greatest on the initial dilatation as opposed to subsequent dilatations.<sup>52, 53</sup> Evaluation of predictive factors for perforation revealed that high distal oesophageal contraction amplitudes (>70 cm H<sub>2</sub>O) were more predominant in those with subsequent perforation.<sup>52</sup> Gastro-oesophageal reflux (GER) occurs in approximately 4–16% of patients after pneumatic dilatation.<sup>18, 54</sup>

The best predictors of success for pneumatic dilatation include older age and a decrease in LES pressure >50% after dilatation.<sup>55–57</sup> The presence of LES pressures >30–50 mmHG, an oesophageal body diameter >3 cm, male gender and pulmonary symptoms appear to be predictors of poorer response.<sup>56–58</sup> Poor emptying on timed barium oesophagogram after dilatation has also been shown to predict which patients may develop recurrent symptoms and require repeat dilatations.<sup>59</sup>

Overall, pneumatic dilatation provides a safe, effective way of decreasing or eliminating the symptoms of achalasia in most patients. When performed, they should be done in a graduated manner and employ commonly used techniques and equipment that the gastroenterologist is familiar. The risk of perforation in experienced hands is small and successful dilatation may obviate the need for more invasive surgery.

## SURGERY

The success of an open Heller myotomy for the treatment of achalasia is well documented.<sup>60</sup> Long-term follow-up has shown that dysphagia relapse rates may be as low as 8–10% from 6 to 9 years after surgery.<sup>60, 61</sup> However, the advent of minimally invasive surgical techniques to treat achalasia has dramatically altered the management algorithm for many gastroenterologists. The advantage of a less invasive, safe and effective surgery entices many gastroenterologists to send their patients to surgery early after the initial diagnosis of achalasia as this obviates the need for dilatation and the inherent risk of oesophageal perforation. This has been reflected in referral patterns noting increased surgical referrals and decreases in the number of pneumatic dilatations being performed.<sup>62</sup>

The standard surgical management for achalasia currently involves a laparoscopic Heller myotomy, which was first reported in 1991.<sup>63</sup> This technique is associated with greater decreases in dysphagia, shorter hospital stays, lower risks of post-operative GER, improved oesophageal emptying and low complications.<sup>38, 64–66</sup> Large series and reviews have demonstrated 90% overall symptomatic improvement following the surgery<sup>18, 38</sup> with >80% remaining dysphagia free at 5 years.<sup>67, 68</sup> The laparoscopic approach is preferred by most over the thoracoscopic approach because of simplicity and similar or improved outcomes.<sup>69</sup>

Despite the overall success rate for symptoms of achalasia after surgical intervention, the presence of GER which may be as high as 36%<sup>54</sup> and recurrent dysphagia are the most common causes of surgical failure. Many studies have evaluated the role of performing an anti-reflux procedure with the laparoscopic Heller myotomy. An early review of 18 articles involving the minimally invasive techniques concluded that anti-reflux surgery portended a better outcome.<sup>70</sup> In contrast to this, a meta-analysis was published in 2003 and included analysis of 21 studies involving 601 patients and concluded that the rates of post-operative GER were not statistically different between those with and without an antireflux procedure.<sup>71</sup> In fact, PPI use among those that undergo fundoplication with the Heller myotomy is 39%.<sup>54</sup> Further data from randomized studies indicate that there is a significant decrease in GER as measured by pH studies in those who underwent fundoplication, but there may not be a decrease in the rate of symptomatic GER.<sup>72, 73</sup> When comparing GER following the pneumatic dilatation vs. postlaparoscopic Heller myotomy, significantly fewer patients take PPI's for GER following a pneumatic dilatation vs. a Heller myotomy.<sup>54</sup> So overall, while a Heller myotomy with fundoplication is safe,<sup>74</sup> the need for the anti-reflux procedure is unknown. Despite this uncertainty, it remains common surgical practice to perform antireflux procedures with the Heller myotomy.

Besides the occurrence of recurrent dysphagia or the development of GER post-operatively, laparoscopic oesophageal myotomy appears to be a safe modality of treatment. Operative complications including mucosal tearing, perforation or post-operative leakage occur in <10% and surgically related death is extremely rare.<sup>64, 70, 72, 73</sup> Surgical therapy after failed pneumatic dilatation has also been shown to be safe and effective although more difficult.<sup>28, 75</sup> New

Table 2. Randomized comparative trials of different treatment modalities in achalasia

Ref no.	Total patient no.	Regimen	Description	Treatment sessions	Immediate remission (%)	~6-month remission (%)	~12-month remission (%)	24-month remission (%)
Botulinum toxin injection vs. pneumatic dilatation								
12	16	Botulinum toxin inj.	100 U	1-2	100			
		Pneumatic dilatation	30, 35 mm	1-3	100			
30	24	Botulinum toxin inj.	80 U	1	75			0*
		Pneumatic dilatation	40-mm Pentax	2	83			50*
77	42	Botulinum toxin inj.	100 U	1-2	64	36	32	
		Pneumatic dilatation	30, 35 mm	1-2	75	75	70	
78	17	Botulinum toxin inj.	60-80 U	2	86	14		
		Pneumatic dilatation	Not reported	1	80	60		
79	39	Botulinum toxin inj.	200 U	1-2	100	89	60	
		Pneumatic dilatation	30, 35 mm	1-2	100	100	100	
80	32	Botulinum toxin inj.	80 U	1	75	63	38	
		Pneumatic dilatation	Witzel	1	94	94	89	
Botulinum toxin injection vs. surgery								
81	80	Botulinum toxin inj.	100 U	2		88	53	34
		Laparoscopic surgery	Heller myotomy/ Dor fundoplication			90	90	88
Botulinum toxin injection vs. surgery								
82	81	Pneumatic dilatation	40-mm Mosher	1-2	49			
		Open surgery	Heller myotomy		79			

dilatations are with microvaxive rigidflex dilators unless noted.  
\* 33 months follow-up.

technology involving computer-enhanced robotic surgery may further minimize the surgical morbidity.<sup>76</sup>

Overall, minimally invasive surgical therapy is safe and effective for the treatment of achalasia. There continues to be controversy regarding the need for an anti-reflux procedure in combination with the surgical myotomy. The current American College of Gastroenterology Practice Guideline recommends surgery as the primary therapy in patients with low surgical risk.<sup>38</sup>

## COMPARATIVE TRIALS

Comparative trials involving the different treatment modalities for achalasia are not common. Obviously, the ideal studies are those that are randomized (Table 2). Studies comparing botulinum toxin injection to pneumatic dilatation reveal that botulinum toxin injection is less efficacious for maintaining symptomatic remission than is pneumatic dilatation. Relapses with botulinum toxin occur both more often and earlier compared with those after pneumatic dilatation even if multiple treatment sessions have been undertaken. As would be expected, both botulinum toxin injection and pneumatic dilatation have less durable response rates compared with surgery. However, a recent non-randomized retrospective study compared pneumatic dilatation vs. laparoscopic Heller myotomy, and demonstrated an early and a late recurrence of dysphagia in both groups of patients with but no significant difference in the overall outcomes over 10 years.<sup>54</sup> This suggests that continued surveillance and treatment of patients long-term is imperative.

## COST-EFFECTIVENESS

Several cost analyses have been performed in an effort to determine which modality for treating achalasia is the most cost-effective. Multiple studies evaluating the cost of the initial 5–10 years of therapy have demonstrated that pneumatic dilatation is the most cost-effective modality in otherwise healthy populations.<sup>83–87</sup> In patients with a other comorbidities that decrease the life expectancy to <2 years, botulinum toxin is more cost-effective.<sup>86</sup> Although surgery may be the most definitive and effective treatment for achalasia, it

appears to be the most costly over the initial years of therapy.<sup>83, 84</sup> More data are needed to determine if it may be more cost-effective than botulinum toxin injection over the long-term as one cost analysis shows that the cost of these two modalities equalizes over the course of 2 years.<sup>88</sup>

## CONCLUSIONS

The aetiology of the pathophysiologic disorder resulting in idiopathic achalasia continues to be poorly understood. The mechanisms of treatment are aimed at alleviating the symptoms of achalasia and not at correcting the underlying disorder. Treatment often involves multiple modalities and in many cases involves combining modalities. Unfortunately, randomized comparative trials are few and thus there remains significant heterogeneity and controversy regarding therapeutic practices for achalasia. Treatment is usually based on both patient and physician factors, preferences, and comfort levels performing the various procedures. Pneumatic dilatation has proven to be a safe, effective and durable modality of treatment when performed by experienced individuals and appears to be the most cost-effective alternative. Endoscopic injection of botulinum toxin is also safe and effective, but the effect diminishes over time and the need for multiple repeat sessions must be considered. This, or pharmacologic therapy, may be the optimal treatment in patients with multiple comorbidities and in older patients. Laparoscopic surgical oesophagomyotomy is a safe and effective modality that can be considered as initial management or as a secondary treatment if the patient does not respond to the less invasive modalities. Continued surveillance in treated patients is imperative as a population of late failures is present with all treatment modalities.

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