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SURGICAL ENDOSCOPY
and Other Interventional Techniques

Botulinum toxin injection vs laparoscopic myotomy for the treatment of esophageal achalasia

Economic analysis of a randomized trial

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Abstract
Background: The treatment of esophageal achalasia is still controversial: current therapies are palliative and aim to relieve dysphagia by disrupting or relaxing the lower esophageal sphincter muscle fibers with botulinum toxin. The aim of this study was to compare the clinical and economic results of two such treatments: laparoscopic myotomy and botulinum toxin injection.
Methods: A total of 37 patients with esophageal achalasia were randomly assigned to receive laparoscopic myotomy (20) or two Botox injections 1 month apart (17). All patients were treated at the same hospital and were part of a larger multicenter study. Symptom score, lower esophageal sphincter pressure, and esophageal diameter at barium swallow were compared. The economic analysis was performed considering only the direct costs (cost per treatment and cost effectiveness, i.e., cost per patient healed).
Results: Mortality and morbidity were nil in both groups. The actuarial probability of being asymptomatic at 2 years was 90% for surgery and 34% for Botox ($p < 0.05$). The initial cost was lower for Botox (€1,245) than for surgery (€3,555), but when cost effectiveness at 2 years was considered, this difference nearly disappeared: Botox €3,364, surgery €3,950.
Conclusion: Botox is still the least costly treatment, but the minimal difference in the longer term does not justify its use, given that surgery is a risk-free, definitive treatment.

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Key words: Achalasia — Laparoscopic Heller myotomy — Botulinum toxin — Cost analysis

The treatment of esophageal achalasia is still controversial [11]: all therapies are palliative and aim to relieve dysphagia by disrupting the lower esophageal sphincter muscle fibers (with an endoscopic balloon or surgical myotomy) or by paralyzing the muscle with botulinum toxin. The latter option has the advantage of a minimal morbidity and low cost, but its efficacy is relatively short-lived. There are only a few clinical randomized trials comparing the efficacy of the different therapeutic options for achalasia [3, 6, 13], and most of them are criticized for their inadequate numerosity, suboptimal treatment techniques, or incorrect randomization. The choice between the different options is consequently often made on the basis of personal preference, availability of local expertise, and data obtained from some large prospective patient series [9, 11, 12, 15]. These data generally favor the surgical option, which reportedly has an 85–95% success rate, but higher social and economic costs. When cost minimization studies were performed, the least costly option was simple endoscopic dilation, while botulinum toxin injection came second [5]. These studies were made using a model based on data available from prospective but nonrandomized studies reported in the medical literature, however. No cost-effectiveness studies based on real life, as obtained from controlled randomized trial, have been published so far.

Three years ago, a multicenter randomized trial comparing laparoscopic myotomy and Botox injection for the treatment of achalasia was begun at six Italian hospitals [14]. One of the aims of this study was to gather data on the different costs in a public health care

Table 1. Preoperative characteristics of patients entering in the trial at the Padova University Hospital

	Surgery (n = 20)	Botox (n = 17)	p value
Median age	47 (20–66)	40 (19–73)	n.s.
Duration of symptoms	24 months (2–20)	26 months (3–240)	n.s.
Median symptom score	17.4 (9–22)	17 (12–22)	n.s.
Median LES pressure	22.5 mmHg (11–36)	34 mmHg (13–49)	<0.05
Median LES nadir pressure	10 mmHg (2.3–24)	13 mmHg (1.1–65)	n.s.
Median esophageal diameter	4 cm (2.5–7)	4 cm (2.5–7)	n.s.

LES, Lower esophageal sphincter

setting and calculate the cost effectiveness (cost per patient cured) of the two treatments. This paper reports the outcome of the economic analysis of that study.

Materials and methods

Inclusion criteria and study design

Symptomatic patients with newly diagnosed achalasia based on clinical, radiographic, and manometric criteria were enrolled in the study from April 2000 to February 2002. Exclusion criteria were age <18 or >75 years; any prior surgical or endoscopic treatment (dilation or botulinum toxin injection); presence of a large, decompensated sigmoid-shaped mega-esophagus; achalasia associated with gastric or esophageal carcinoma; neuromuscular disorders; pregnancy; severe cardiovascular disability or coagulopathy; or any severe contraindications for general anesthesia. All patients signed an informed consent form, and the study protocol was approved by the Ethical Committee of the University of Padova School of Medicine.

Eligible patients were randomly assigned to receive two injections of 100 units of botulinum toxin A (Botox, Allergan, Irvine, CA, USA) 1 month apart [1] or laparoscopic Heller myotomy. Patients were reevaluated at 6 months, 1 year, 18 months, and 2 years, and they were instructed to call if their symptoms worsened in the interval between two checkups. Patients who failed to benefit from laparoscopic myotomy were offered a pneumatic endoscopic dilation, and those who failed to benefit from Botox injection were offered laparoscopic myotomy.

Symptom evaluation

Clinical data were collected from each patient by means of a questionnaire, and the patient's symptoms were scored according to severity and frequency. The symptom score for dysphagia and regurgitation was calculated by combining the severity of each symptom (dysphagia: 0 = none, 2 = mild: sensation of passage of food through the cardia, 4 = moderate: need to drink liquid in order to swallow, 6 = severe: obstructing dysphagia; regurgitation: 0 = none, 2 = mild: after straining or large gulps, 4 = moderate: with changes in body position, 6 = severe: aspiration) with the frequency (0 = never, 1 = occasionally, 2 = once a month, 3 = once a week, 4 = twice a week, 5 = daily); the highest score obtainable was 22. A treatment was considered as having failed when the patient's symptom score exceeded the 10^{th} percentile of the pretreatment score obtained from a database of >100 laparoscopically treated achalasia patients [15], so the threshold for defining treatment failure was 9.

Physiological studies and barium swallow

Stationary manometry, post-treatment 24-hour pH monitoring and barium swallow were performed as described in detail elsewhere [8, 15].

Technical details of the treatments

The techniques for Botox injection and laparoscopic Heller myotomy have been described in detail elsewhere [1, 15]. In brief, 100 units of botulinum toxin A were injected radially through a 25-gauge sclerotherapy needle in eight aliquots, four at the gastro-esophageal junction and four ~1 cm above, during an upper gastrointestinal endoscopy performed under mild sedation with midazolam. Patients were allowed to eat on the same day and were treated as "day-hospital" cases (no overnight stay). A laparoscopic myotomy 6–8 cm long and extending to the first 1–2 cm on the gastric side was performed on the anterior part of the esophagus, and an anterior partial fundoplication (Dor) was used to prevent gastroesophageal reflux.

Statistical analysis

Data are expressed as medians and ranges. Differences between measurements in the two groups and within each group were compared using nonparametric tests (Wilcoxon and Mann-Whitney, as appropriate). The cumulative remission rates of each treatment were estimated by the actuarial method, and the difference between treatment groups was estimated by the log-rank test. A probability of $<5\%$ was assumed to be statistically significant ($p < 0.05$).

Economic analysis

In this study, the cost analysis was performed in one of the centers (Padova) and was applied only to patients enrolled and treated at that center, considering only the direct costs (hospital costs). Indirect costs, such as nonmedical services relating to the treatment (e.g., transportation and family care, and indirect morbidity costs such as absence from work for hospitalization and convalescence) were not assessed. Hospital costs were calculated using the Activity-Based Costing (ABC) method, which is a full costing system that considers treatment as a production process and calculates the cost of each microstep involved in the process as a whole (e.g., the costs of a single blood test, disposable instruments, operating room time). The cost of personnel (medical doctors and nurses) was based on the standard cost indicated in the Hospital Budget per person per year, calculating the cost per minute (0.99 Euros for doctors and 0.31 Euros for nurses). The minutes spent on each step of the process (operating time or Botox injection) were recorded, and the cost of each diagnostic procedure (manometry, 24-hour pH monitoring, upper G.I. endoscopy, barium swallow) was calculated according to the Veneto Regional Authority's prices for these procedures in 1998. For the pre- and postoperative period, it was assumed that each patient needed 30 min of a doctor's and 60 min of a nurse's work per day. The day-hospital admission cost was assumed as half of a full-day admission.

Two parameters were ultimately compared: the cost of the treatment (defined as the cost of the original treatment plus the cost of any retreatment in the event of failure) and the cost effectiveness of each treatment (defined as the cost of each option—surgery or Botox—divided by the number of patients cured at each time interval), calculated according to the formula:

$$\frac{\text{Cost of treatment}}{1 - \text{Probability of being symptomatic at each interval}}$$

Results

Eighty patients with naive achalasia joined the study at five Italian centers; 40 were randomized to receive Botox

Table 2. Cost of treatment expressed in Euros

Laparoscopic myotomy	
Diagnosis and preoperative work-up	361
Treatment	2,333
Post-operative course	861
Total	3,555
Botulinum toxin	
Diagnosis and preoperative work-up	250
Treatment	616
Post-operative course	379
Total	1,245
Endoscopic dilation	
Diagnosis and preoperative work-up	250
Treatment	310
Post-operative course	379
Total	939

[a] 1 Euro = $1 US

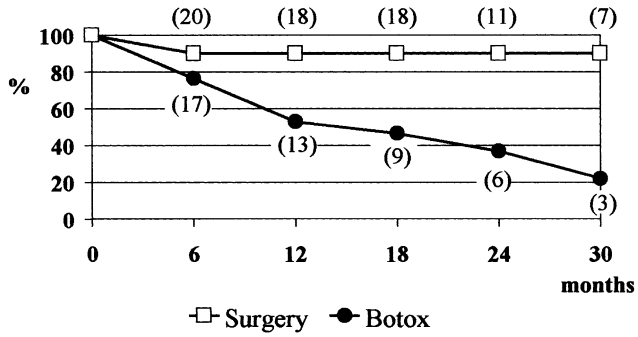

Fig. 1. Probability to be asymptomatic at 30 months after laparoscopic Heller myotomy and after Botox treatment. At 30 months, only 22% of patients are expected to remain asymptomatic after Botox treatment, compared to 90% of the operated patients. In parentheses: the number of patients at risk for each interval time.

treatment and 40 to undergo laparoscopic cardiomyotomy. Thirty-seven of the 80 patients were seen at Padova University Hospital and formed the study population: 20 patients were randomized to undergo laparoscopic myotomy and 17 to have Botox injections. Table 1 summarizes the demographic, clinical, radiological, and manometric features of this group. The median follow-up was 17 months (range 12–34). At present, all patients have a follow-up of at least 12 months and 16 have a follow-up of 2 years or more. Mortality was nil in both treatment groups, and no complications were observed in either. The median hospital stay was 6 days (range 3–6) in the surgical group; patients who had Botox injections were treated as "day hospital" cases with no overnight stay.

Clinical results

Immediately after treatment, the two groups of patients improved in much the same way and no differences were observed in symptom recurrence during the first 6 months. The Botox group's results deteriorated rapidly thereafter, however, and a year after treatment nearly 50% of them were symptomatic again. The likelihood of remaining asymptomatic at 2 years is shown by the actuarial curve for the two treatments: at 30 months, the chances of being cured were 90% for patients treated by laparoscopic myotomy but 22% for those treated with Botox injections (Fig. 1).

Physiological studies and barium swallow findings

At the 6-month check-up, esophageal manometry showed a similar reduction in LES resting and nadir pressure in both groups. Six months after treatment, 24-h pH monitoring of the distal esophagus revealed abnormal acid exposure in 1/20 patients in the laparoscopic group and none of the 15 patients in the Botox group (two patients refused to undergo pH monitoring). The esophageal diameter measured at barium swallow decreased significantly in the surgical group, but only minimally in the Botox group (Fig. 2).

Subsequent clinical course

All 11 patients with recurrent symptoms after the Botox injections underwent laparoscopic myotomy; the postoperative course was uneventful, and they are all asymptomatic. Both patients who had recurrent symptoms after laparoscopic myotomy were treated with three and one endoscopic dilations, respectively, and are asymptomatic at the present time.

Economic evaluation

Table 2 shows the cost breakdown for laparoscopic myotomy, Botox injections, and endoscopic dilations. As expected, the initial cost of laparoscopic myotomy was nearly three times higher than Botox treatment (3,555 vs 1,245 Euros). Much of this cost was due to operating room costs and postoperative hospital stay. The final cost of the treatment per patient (first treatment plus any retreatment) was 3,743 Euros for laparoscopic myotomy and 3,549 Euros for Botox treatment.

The cost effectiveness of the two treatments changed considerably with time: At 6 months, when the outcome of the two treatments was similar, Botox seemed more cost-effective, but the cost of Botox per patient cured had doubled after 1 year of follow-up and tripled at 2 years (Fig. 3). The cost-effectiveness ratio of Botox vis-à-vis surgery thus dropped from 2.8:1 at the beginning of the observation period to 1.2:1 at 2 years, indicating that in the long run, laparoscopic myotomy is almost as cost effective as Botox injection for treating achalasia.

Discussion

The rarity of achalasia and the consequent difficulty in performing randomized controlled trials has led to a customer-based (patient or physician), rather than an evidence-based choice of treatment. The factors that usually influence this choice are the availability of surgeons skilled in performing laparoscopic myotomy or endoscopists expert in performing balloon dilation; the

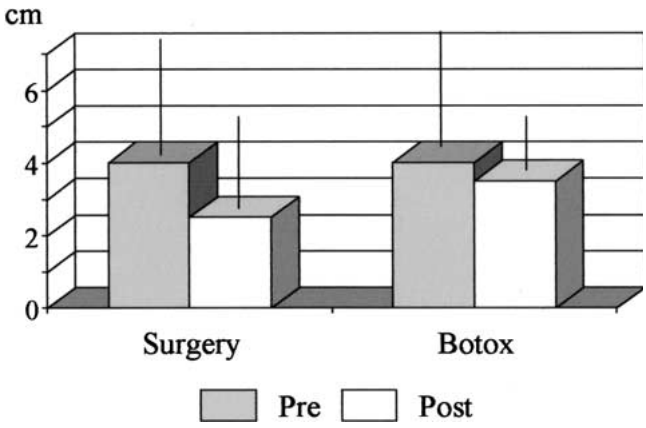

Fig. 2. Median esophageal diameter before and after the treatment in the two groups of patients. Only after surgery a significant reduction of the diameter of the gullet was observed. In the surgical group the diameter decreased from 4 cm (2.5–7.0) to 2.5 cm (1.6–4.5), $p < 0.05$; in the Botox group the diameter decreased from 4 cm (2.5–7.0) to 3.5 cm (1.8–4.5), p = n.s.

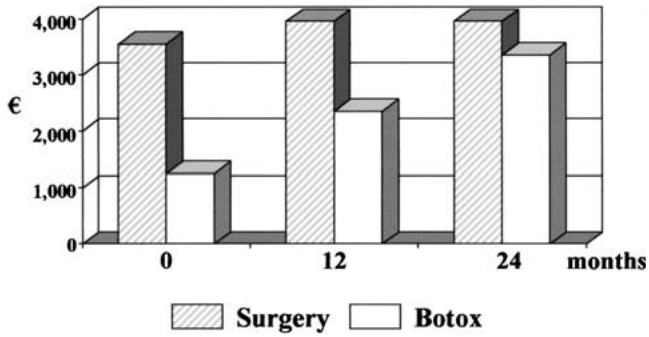

Fig. 3. Cost effectiveness of surgery versus Botox injections at 6, 12, and 24 months after the treatment. The ratio, roughly 3 to 1 at the beginning of the observation period, approaches 1:1 after 2 years.

physician's and patient's propensity to risk; and, last but not least, the cost of the procedure [7]. So far, in Italy, though there are no official data based on an achalasia registry, the impression is that Botulinum toxin is offered as the first option for achalasia at most small to medium-sized hospitals (more and more patients arrive at our referral center after being treated once or twice with Botox elsewhere). This is because the Botox treatment is virtually complication- and risk-free for the patient (and consequently carries no risk of litigation related to the procedure), and the toxin injection method is simple and manageable for any endoscopist, whereas endoscopists avoid pneumatic dilation because of the perforation risk, and only major centers have expert laparoscopic surgeons performing laparoscopic myotomy. Moreover, the way in which the Italian National Health System refunds hospitals is based on a system that often underestimates the cost of expensive procedures (i.e., surgery) and overestimates the less costly endoscopic treatments.

The present study shows, however, that laparoscopic myotomy is also a no-risk procedure: No surgery-related complications were observed in the 20 patients operated in Padua, and only one minor complication (bleeding from one of the trocar sites) was recorded among the 40 patients in the laparoscopic myotomy arm of the multicenter trial [14]. Although there were no complications relating to surgical procedure, the hospital stay for laparoscopic myotomy was quite long (6 days). This can be explained by the fact that, since surgery was concentrated in two hospitals, most of the patients lived outside the area where the hospital was located. These patients consequently all had preoperative studies (manometry and barium swallow) as inpatients and, after surgery, though most of them could have been discharged within 48 h, they preferred to stay a day longer in hospital (free of charge in our public health system) rather than go into a hotel (at their own expense).

Moreover, laparoscopic myotomy achieves very consistent and durable results: The 90% chance of being asymptomatic at 2 years recorded in this study is entirely comparable with data reported in the medical literature [2, 4, 9, 10, 15], and these results remain stable at least in the medium term, since most failures are apparent within the first 6 months after surgery and are probably related to technical problems (inadequate myotomy) [16]. Conversely, even when the timing and dosage (two 100-IU) injections each, 1 month apart reportedly have an 80% success rate at 1 year [1], Botox injection shows a rapid loss of efficacy with $<40\%$ probability of remaining asymptomatic after 24 months.

Botox injection was the less expensive option in our trial. though treatment costs are very difficult to compare in different health care systems (mainly private in the United States public in the United Kingdom, Sweden, or Italy, mixed in France), the cost of Botox treatment was similar in the United States and Italy, while a much larger difference was observed for the cost of surgery, with a cost in Italy 60% lower than in the United States [5], though this did not prevent laparoscopic myotomy from costing three times as much as Botox injections in Italy as well. This difference fades (just 103 Euros in favor of Botox), however, if the cost of retreatment is considered, and even this minimal advantage will probably disappear when the observation period extends to 3 years or more.

From a purely economic standpoint, Botox remains less costly, but one may wonder to what degree the economic aspects should influence the choice of treatment: though still slightly more expensive than Botox when 2-year cost-effectiveness is considered, laparoscopic myotomy is a safe, effective, one-off therapy for esophageal achalasia, whereas Botox has to be repeated at least once—and often more—when symptoms recur (though the consequences of repeated injections and the potential influence of multiple injections on subsequent treatments are not known), or else a surgical or endoscopic alternative has to be adopted. The main problem of surgery remains the lack of properly trained surgeons for this operation at many hospitals, but given the rarity of achalasia, concentrating the cases in a few specialist centers should not be a major economic issue.

This economic analysis showed only a marginal economic advantage of Botox, and the clinical results of the larger study clearly demonstrate that myotomy is more effective, so Botox should not be offered to low-risk achalasia patients; its use should be restricted to patients unfit for surgery. It is time for the surgical and

gastroenterological communities to arrange a multicenter European randomized controlled trial comparing these two treatments, also covering the economic aspects, in order to provide a rational answer to the long-standing dilemma: to dilate or to operate for achalasia?

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