Randomized Controlled Trial of Botulinum Toxin Versus Laparoscopic Heller Myotomy for Esophageal Achalasia

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Objective: To compare laparoscopic cardia myotomy and fundoplication with botulinum toxin (BoTx) injection in patients with esophageal achalasia.

Summary Background Data: Although myotomy is thought to offer better results, recent studies have reported 80% success rates after 2 BoTx injections a month apart. No randomized controlled trials comparing the 2 treatments have been published so far.

Materials and Methods: Newly diagnosed achalasia patients were randomly assigned to BoTx injection or laparoscopic myotomy. Symptoms were scored; lower esophageal sphincter resting and nadir pressures were measured by manometry; barium swallow was used to assess esophageal diameter pre- and post-treatment. Eight to one hundred units of BoTx were injected twice, a month apart, at the esophagogastric junction. Myotomy included anterior partial (Dor) or Nissen fundoplication.

Results: Eighty patients were involved in the study: 40 received BoTx and 40 underwent myotomy. Mortality was nil. One surgical patient bled from the trocar site. Median hospital stay was 6 days for surgery; BoTox patients were treated as day-hospital admissions. All patients completed the follow-up. After 6 months, the results in the 2 groups were comparable, although symptom scores improved more in surgical patients (82% confidence interval [CI] 76–89 vs. 66% CI 57–75, $P < 0.05$). The drop in lower esophageal sphincter pressure was similar in the 2 groups; the reduction in esophageal diameter was greater after surgery (19% CI 13–26 vs. 5% CI 2–11, $P < 0.05$). Later on, symptoms recurred in 65% of the BoTx-treated patients and the probability of being symptom-free at 2 years was 87.5% after surgery and 34% after BoTx ($P < 0.05$).

Conclusion: Laparoscopic myotomy is as safe as BoTx treatment and is a 1-shot treatment that cures achalasia in most patients. BoTx should be reserved for patients who are unfit for surgery or as a bridge to more effective therapies, such as surgery or endoscopic dilation.

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Achalasia is a relatively rare disease of the esophagus characterized by the loss of esophageal body peristalsis and incomplete relaxation of the lower esophageal sphincter (LES). A selective loss of inhibitory nerve endings at myenteric plexus level is the neuromuscular abnormality that probably lies behind this disease: this functional damage is irreversible, and the treatment of esophageal achalasia is only palliative, aiming to reduce the pressure gradient across the LES and facilitate the passage of the bolus. A reduction in LES pressure can be obtained by disrupting the LES muscle fibers with forceful endoscopic pneumatic dilations, by cutting the muscle fibers (myotomy), or by poisoning them with botulinum toxin (BoTx). BoTx is a powerful poison that takes effect by blocking the acetylcholine release from nerve endings: this blockade at LES level in achalasia patients counterbalances the selective loss of inhibitory neurons and enables sphincter relaxation (or at least a drop in pressure). This new approach to achalasia treatment was proposed by Pasricha[1] in the early nineties: dysphagia regression was reported in nearly 80% of patients in the short term and in 50% at 6 months, but patients needed repeated BoTx injections to remain asymptomatic.[2,3] More recently, however, Annese

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and D'Onofrio used a different modality of administration and reported an 80% success rate at 12 months in patients receiving 2 injections of BoTx within a 4-week interval,[4,5] thus arousing new interest in this therapy.

Meanwhile, a laparoscopic approach has been proposed for performing the surgical myotomy of the LES fibers in achalasia patients.[6] Laparoscopic myotomy has gained widespread popularity for its relatively limited invasiveness because it is a 1-shot therapy and it has an encouraging success rate of 85% to 90%.[7,8] Opponents of the laparoscopic option argue that laparoscopic myotomy, although less invasive than open surgery, is still invasive, risky for patients and expensive, and it requires surgical skills that are not always available (and the results of laparoscopic myotomy depend largely on the surgeon's expertise); on the other hand, BoTx treatment is less expensive, virtually risk-free, easily administered by any endoscopist, and the results of the treatment seem to be reproducible.[4]

We decided therefore to compare the short- and medium-term efficacy of BoTx injection and laparoscopic myotomy in a randomized group of achalasia patients without any previous treatment. The main goals of the present study were to assess the number of patients who remained symptom-free at 1 year, the actuarial probability of being asymptomatic at 2 years after Botox injection or laparoscopic myotomy and to measure these results objectively by means of esophageal manometry, barium swallow and 24-hour pH monitoring of the distal esophagus.

MATERIALS AND METHODS

Patients

Symptomatic patients with newly diagnosed achalasia based on clinical, radiographic, and manometric criteria were enrolled in the study from April 2000 to February 2002. Criteria for inclusion were achalasia, defined as incomplete or absent LES relaxation and the absence of peristaltic contractions in the esophageal body at manometry and the presence of a dilated esophagus with bird's beak shaped narrowed cardia at barium swallow. Exclusion criteria were age under 18 or over 75 years, any previous 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 Committees of the University of Padova School of Medicine and of the other institutions involved.

Study Design

The study was a randomized trial comparing clinical and objective parameters of improvement in patients treated with botulinum toxin injection or laparoscopic cardiomyotomy (Fig. 1). All patients underwent a standardized pretreatment evaluation including clinical symptom assessment, esophageal manometry, barium swallow, and upper gastrointestinal endoscopy to rule out any malignancies or a secondary cause of achalasia.

Eligible patients were randomly assigned using a computer-generated random number to receive an injection of 100 units of botulinum toxin A (Botox, Allergan Inc., Irvine, CA) or laparoscopic Heller myotomy; stratification according to age and sex was performed by the coordination center. In the case of BoTx injection, patients who had a good symptomatic response (50% reduction of the symptom score) received a second botulinum toxin injection 4 weeks later, according to the protocol of Annese et al.[4] Patients who had no symptomatic improvement after the first injection were considered as early failures or nonresponders. Patients were re-evaluated at 6 months, 1 year, 18 months, and 2 years, and they were instructed to call if their symptoms worsened in the interval between 2 check-ups.

Symptom Assessment

Clinical data were collected from each patient by means of a questionnaire, and the patients' symptoms were scored according to severity and frequency. The symptom score for dysphagia and regurgitation was calculated by combining the severity of each symptom (0 = none, 2 = mild: sensation of passage of food through the cardia, 4 = moderate: need to drink liquid to swallow, 6 = severe obstructing dysphagia) 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 a failure when the patient's symptom score exceeded the 10th percentile of the preoperative score, obtained from a previous database of more than 100 laparoscopically treated

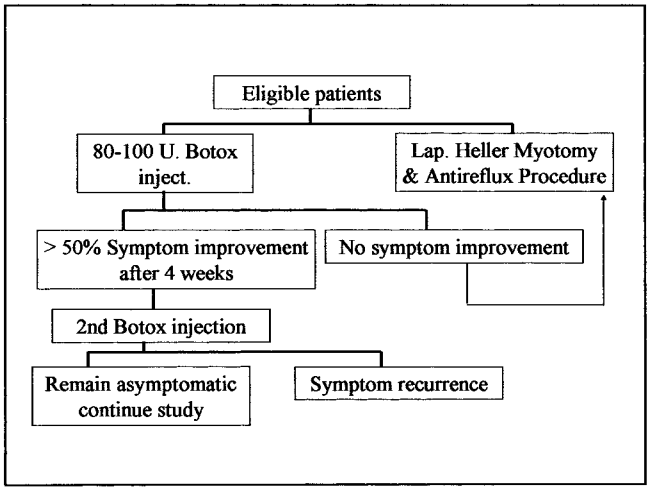

FIGURE 1. Flow-chart illustrating the study protocol.

achalasia patients,[7] so the threshold score for defining a treatment failure was 9. (The score of 9 roughly corresponds to an Eckardt score of 3.)

Esophageal Manometry

Stationary manometry of the esophagus was performed before and 6 months after the treatment and whenever a patient had recurrent symptoms by using a pneumohydraulic perfusion system. The LES pressure was calculated by averaging the pressures recorded by 4 side holes positioned at the same level, 90° apart, and withdrawing the catheter twice using a motorized pull-through technique at a constant speed of 1 mm/s, from the stomach to the esophageal body, passing through the high-pressure zone (the LES pressure was therefore the average of 8 pressure recordings). The LES pressure was calculated as the midexpiratory pressure at the respiratory inversion point. Esophageal body motility and LES relaxations were assessed by recording the pressure changes elicited by 10 wet swallows (10 mL of water) with the side holes of the catheter positioned inside the LES and 5, 10, 15, and 20 cm higher up, according to the technique described elsewhere.[9] The residual LES pressure was defined as the minimum pressure (nadir) recorded in the LES during swallowing.[9] Patients with a median esophageal body contraction amplitude (recorded in the distal 2 side holes) greater than 40 mm Hg were considered as having vigorous achalasia.[10]

Twenty-four Hour Esophageal pH Monitoring

Twenty-four hour pH monitoring was only performed 6 months after treatment to evaluate any abnormal gastroesophageal reflux by positioning a glass electrode 5 cm above the upper border of the LES according to the standard procedure reported elsewhere.[11] Traces from patients with abnormal reflux on computerized analysis were carefully reviewed to distinguish true episodes of gastroesophageal reflux from false reflux caused by stasis.[12]

Barium Swallow

A barium esophagogram was obtained in the upright position before treatment, 1 month, and 1 year after treatment, and whenever a patient complained of symptom recurrence. Patients swallowed a glass of low-density barium sulfate suspension, then radiograms were obtained in the anteroposterior and slightly left posterior oblique positions: the maximum esophageal diameter was measured at the site of the barium air level.

BoTx Injection

Upper gastrointestinal endoscopy was performed under mild sedation using midazolam. The esophagogastric junction was identified and 100 units of botulinum toxin A (Allergan Inc) was injected radially through a 25-gauge sclerotherapy needle (5 mm long) in 8 aliquots, 4 at the gastroesophageal junction and 4 additional injections approximately 1 cm above. Responsive patients were reinjected with an identical dose 4 weeks later.[4] Patients were allowed to eat on the same day and were treated as "day-hospital" cases. To ensure that the same procedure was used in all the 5 centers participating the study, the first 2 patients randomized to receive BoTx injections at the main center (Padova) were treated under the supervision of the endoscopist most experienced in this procedure (V.A.) in the presence of all the other endoscopists taking part in the trial.

Surgical Procedure

Surgery was centralized in 3 of the 6 participant centers and performed by surgeons with experience of more than 20 laparoscopic myotomies for esophageal achalasia.[7,13] A laparoscopic myotomy 6 to 8 cm long was performed on the anterior part of the esophagus; the myotomy was extended 1 to 2 cm on the gastric side, according to a technique described in detail elsewhere.[5] The techniques adopted differed slightly in that a Rigiflex 30 mm balloon lightly inflated with 40–60 mL of air was used inside the esophagus during the myotomy in one center to better stretch the circular fibers, whereas an endoscope and intraoperative manometry were used in the others to identify any residual high-pressure zone at myotomy level. Moreover, a total fundoplication (floppy Nissen) was used in 2 centers to prevent gastroesophageal reflux as opposed to an anterior partial fundoplication (Dor) in the other.[7,13] Because there are no data to support a clear-cut superiority of one technique over the other—at least in the midterm follow-up—surgeons were allowed to adopt their preferred technique.[14]

Statistical Analysis

Sample size was calculated assuming a beta error of 15%, an alpha error <0.05, and a difference between the 2 treatments of 30%. According to these calculations, 80 patients were needed for the study. Data are expressed as median and ranges. Percentage changes are expressed as means and 95% confidence intervals. The results were assessed on an intention-to-treat basis. Differences between measurements in the 2 groups and within each group were compared using nonparametric tests (Wilcoxon and Mann–Whitney, as appropriate). Fisher exact test was used to compare categorical data. 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 ($P < 0.05$).

RESULTS

Patient Demographics and Clinical Characteristics

Ninety-one patients were observed: 11 patients were not enrolled because of age (4), previous treatment (4),

decompensated esophagus (1), and refusal to take part in the study (2). Eighty patients with naive achalasia joined the study: there were 36 males and 44 females with a median age of 50 (range, 18–73) years. Forty patients were randomized to receive BoTx treatment and 40 to receive laparoscopic cardiomyotomy. Table 1 summarizes the demographic characteristics of the 2 groups. Twenty-four patients in the BoTx group and 17 in the surgical group were over 50 years of age (P = n.s.). The clinical, radiologic, and manometric characteristics of the 2 groups are summarized in Table 1: no differences were observed except for the resting LES pressure, which was higher in the BoTx group. Seven patients in the BoTx group and 8 in the surgical group had "vigorous achalasia" (P = n.s.). The median follow-up was 23 months (range, 12–34). At present all patients have a follow-up of 12 months and 37 patients have a follow up of 2 years.

Mortality, Morbidity, and Hospital Stay

There was no mortality in any of our patients. No complications were observed in the BoTx group, apart from transient retrosternal pain in 4 patients. In the surgical group, bleeding from the trocar site occurred in one patient (2.5%; P = n.s.), who required revisional surgery, but no transfusions. The median hospital stay was 6 days (range, 4–10) in the surgical group; patients who had BoTx injections were treated as "day hospital" cases and were discharged in the afternoon. Though not fully comparable, the difference can be considered statistically significant in favor of the BoTx group.

Clinical Response to Treatment

Immediately after the treatment, the 2 groups of patients improved in much the same way and no differences were observed in symptom recurrence during the first 6 months. Six months after the treatment, both groups had a statistically significant reduction in dysphagia and regurgitation symptoms, but surgical patients had a greater reduction in their scores, expressed as a percentage, ie, 82% (confidence interval 76–89) as opposed to 66% (confidence interval 57–75) after BoTx injection, $P < 0.05$. The BoTx group's results deteriorated rapidly thereafter, however, and a year after the treatment nearly 40% of them were symptomatic again. The likelihood of remaining asymptomatic at 2 years is shown by the actuarial curve for the 2 treatments: at 24 months, 87.5% of patients treated by laparoscopic myotomy were asymptomatic versus 34% of those treated by BoTx (Fig. 2).

Physiological Studies and Barium Swallows Results

At the 6-month check-up, esophageal manometry showed a similar reduction in LES resting pressure in both groups (Fig. 3). The reduction in LES resting pressure (expressed as a percentage reduction with respect to the situation before treatment) was slightly greater in the surgical group, but the difference was not statistically significant. The nadir LES pressure at swallowing was significantly lower in both groups (Fig. 4): 78% of myotomized patients had a nadir pressure at swallowing lower than 7 mm Hg (the normal value at our esophageal laboratories) versus 62% of patients who had BoTx injection (P = n.s.). Patients who developed recurrent dysphagia (after BoTx injection or surgery) always had a nadir LES pressure higher than those whose treatment was successful (Fig. 5).

Six months after treatment, 24-hour pH monitoring of the distal esophagus revealed 1 of 39 patients in the laparoscopic group with abnormal acid exposure and none of the 35 patients in the BoTx group (5 patients refused the pH-monitoring test). When the trace was reviewed, however, it was considered a "false reflux." Esophageal diameter, as mea-

TABLE 1. Demographic, Clinical, Manometric, and Radiological Characteristics of the 2 Groups of Patients

	Surgery		BoTx		
		Range		Range	*P*
Patients	40		40		
Male	18		18		
Female	22		22		
Median age	48	(18–71)	55	(19–73)	n.s.
Duration of symptoms	24 months	(2–240)	18 months	(2–240)	n.s.
Median symptom score	17.5	(6–22)	17	(8–22)	n.s.
Median LES pressure	27 mmHg	(11–51)	36 mmHg	(13–65)	<0.05
Median LES nadir pressure	10 mmHg	(2.3–24)	13 mmHg	(1.1–65)	n.s.
Median esophageal diameter	4.1 cm	(2.5–7)	3.5 cm	(2,5–7)	n.s.

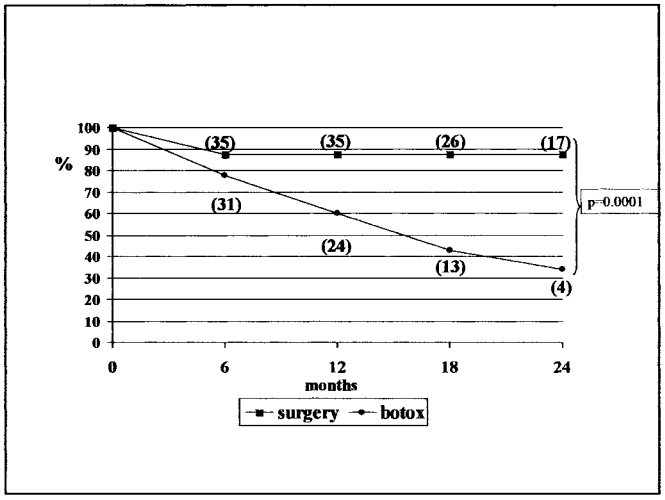

FIGURE 2. Probability of remaining asymptomatic after treatment (patients at risk for each interval in brackets). The 2 curves differ significantly ($P < 0.01$).

sured by barium swallow, decreased significant in the surgical group, but only minimally in the BoTx group (Fig. 6).

Predictors of Response

Posthoc evaluation failed to demonstrate any predictive factor of good response. In particular, sex, age <50 years, presence of vigorous achalasia, and duration of symptoms could not distinguish patients with a favorable outcome in either group. In the surgical group, 2 of 20 failures occurred in the subgroup that received an anterior fundoplication according to Dor and 3 of 20 in the subgroup that had total 360° Nissen fundoplication, P = n.s.

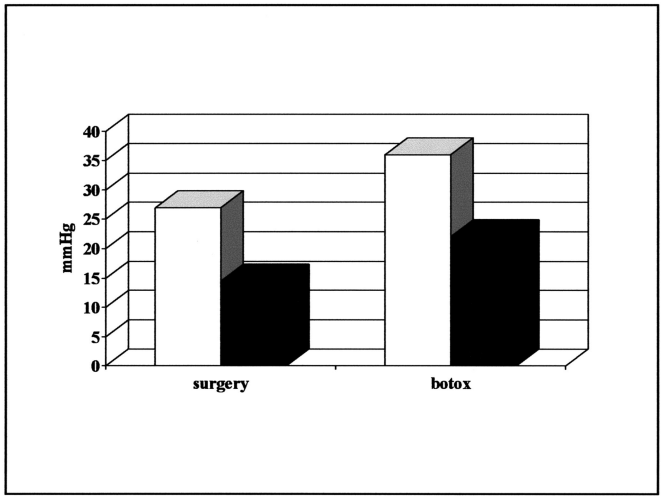

FIGURE 3. LES resting pressure in patients before and 6 months after myotomy or BoTx injection. White column = pretreatment values; black column = post-treatment. In both groups the pressure decreased significantly; from 27 mm Hg (11–51) to 14.50 mm Hg (3.5–35) for surgery ($P < 0.05$), and from 36 mm Hg (13–65) to 22 mm Hg (12–50) for BoTx ($P < 0.05$), respectively. Values are expressed as median and (ranges). Pretreatment values were higher for BoTx compared with surgery, but no difference was observed between myotomy and BoTx post-treatment values.

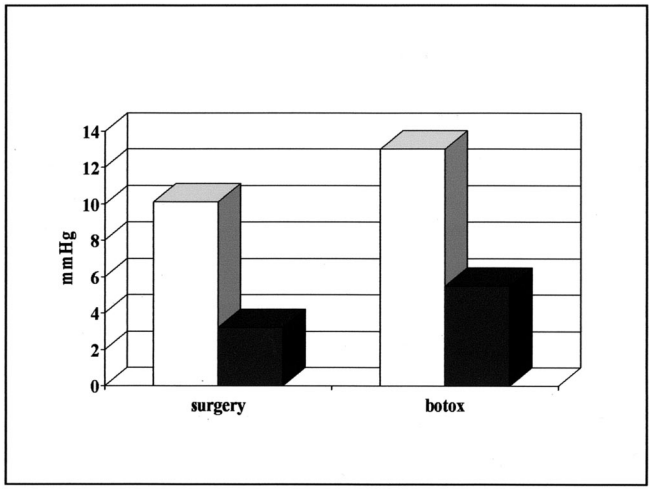

FIGURE 4. Lowest LES pressure at swallowing (nadir pressure) in patients before and 6 months after myotomy or BoTx injection. White column = pretreatment values; black column = post-treatment. In both groups, the pressure dropped significantly: from 10.1 mm Hg (2.3–24) to 3.2 mm Hg (0–11.2) for surgery ($P < 0.05$) and from 13 mm Hg (1.1–65) to 5.5 mm Hg (0–40) for BoTx ($P < 0.05$), respectively. Values are expressed as median and (ranges).

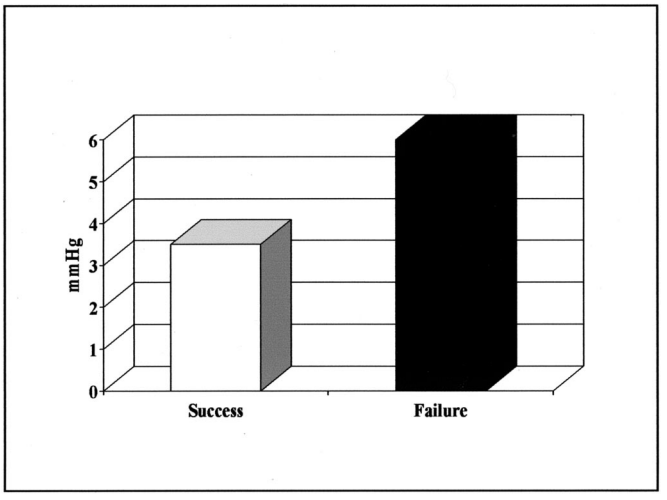

FIGURE 5. Lowest LES pressure at swallowing (nadir pressure) in responders and nonresponders to both treatments. Nadir pressure in responders (white column) was 3.5 mm Hg (0–40); in nonresponders it was 6 mm Hg (0–12; P = n.s.). Values are expressed as median and (ranges).

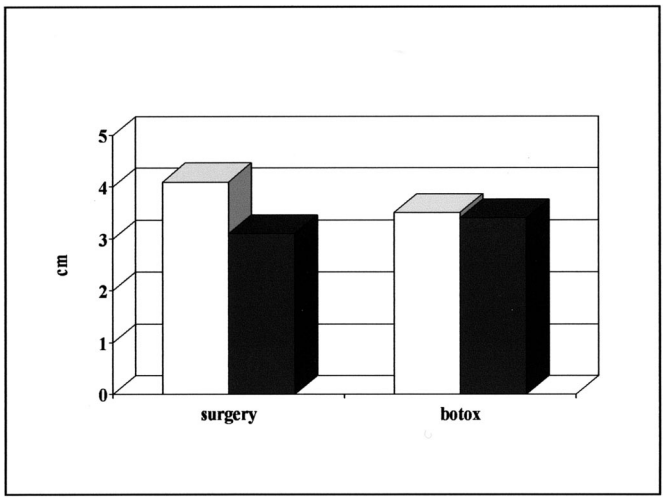

FIGURE 6. Largest esophageal diameter at barium swallow before and after myotomy or BoTx injection. White column = pretreatment; black column = post-treatment. The values (cm) are: premyotomy 4.1 (2.5–7) post 3.1 (1.7–4.5); pre Botox 3.5 (2.5–7); post 3.4 (1.8–5.1). Values are expressed as median and (ranges). The difference between before and after treatment was only significant for surgery ($P < 0.05$).

Subsequent Clinical Course

Of the 25 patients with recurrent symptoms after BoTx injections, 10 subsequently had laparoscopic myotomy (9 are asymptomatic), 7 had further toxin injections, 1 had endoscopic dilation, and 7 are still considering further treatment. Of the 5 patients with recurrent symptoms after surgery, 2 had pneumatic dilations and are currently asymptomatic and 3 are still considering further treatment.

DISCUSSION

Although the etiology of achalasia remains elusive, the medical community learned some time ago how to palliate its main symptoms, dysphagia and regurgitation. Leaving aside the cardia divulsion with a whale bone performed by Willis in the 17th century,[15] forceful dilations have been reported since 1923[16] and cardiomyotomy was described by Heller at the beginning of the last century.[17] Botulinum toxin joined the physician's armamentarium many years later, prompting great enthusiasm for its safe and simple use: there are practically no reports of any severe complications after BoTx injection in the cardia. Achalasia is a rare disease, however, and there are no well-documented properly sized controlled, randomized clinical trials on the different therapeutic options available.

In designing this trial, one of the major concerns was that injecting the toxin in the cardia submucosa might make myotomy more difficult or hamper the final outcome.[18] However, despite a subjective impression that myotomy would be more difficult, we did not found in our previous experience any objective evidence in terms of higher rates of perforation, conversion to open surgery or late symptom recurrence[19] and even the medical literature is controversial on this issue.[20,21] Nonetheless, we chose a protocol with 2 injections of BoTx with a relatively short interval between them and no further repetition of the treatment in the event of relapsing dysphagia to avoid excessive damage to the submucosal plane. It is worth noting, however, that this modality of BoTx administration offered better results, in terms of symptom relief, than multiple BoTx injections when symptoms recurred.[4,5]

The main goals of the study were to establish which treatment was safer, achieved better symptom control, and objectively lowered the LES pressure and reduced the esophageal diameter more. Both treatments were equally safe: no adverse effects were encountered in the surgical group apart from minimal bleeding from a trocar site requiring revisional surgery but no transfusion. This was the only patient who remained 10 days in the hospital; the median hospital stay was 6 days for surgical patients (but it should be noted that most patients lived far from the 2 hospitals concerned and, in a public health system, such patients prefer to stay a day longer, free of charge, in hospital rather than go into a hotel).

The response to the BoTx treatment was initially the same as for surgery and all patients reported a drop in their symptom scores, but after 6 months myotomized patients already had a greater improvement in symptom score and soon afterward dysphagia and regurgitation recurred in nearly half of the patients treated with BoTx. The likelihood of symptom recurrence in our BoTx group was 40% at 1 year, a figure coming between the results reported by Vaezi (32%)[22] and Annese (80%).[4] Surgical patients, on the other hand, had an 87% chance of remaining symptom-free at 1 year, and this is much more consistent with other findings in the medical literature.[7,8,23,24] The variability of reported results with toxin injections might be explained by differences in clinical assessment (with more or less stringent criteria to determine clinical remission), or differences in the BoTx administration method or bioavailability, or different individual responses to the toxin. Conversely, the results obtained by experienced and trained surgeons are highly consistent, demonstrating that—once it has been fully mastered—the surgical technique is perfectly reproducible and always produces the same results.[25] In the present study, all recurrences after surgery occurred within 6 months of the operation and were probably the result of an incomplete myotomy (the most common cause of failure).[26] Differences in surgical technique (eg, type of fundoplication to prevent reflux) did not seem to affect the final results, at least in the medium term.[23] A progressive decline in the efficacy of myotomy with Nissen fundoplication has been reported, but this occurred later in the follow-up.[27]

In the present study, both treatments achieved a reduction in LES resting and nadir pressures at swallowing, though

the LES pressure reduction was greater after surgery. In other studies using BoTx, the LES pressure did not change: this might depend on the repeated, higher dose used in our trial. Moreover, all patients whose symptoms relapsed (irrespective of type of treatment) achieved a less marked LES pressure reduction than those who did well, confirming that LES pressure reduction is a key point in achalasia treatment.

As observed by Vaezi et al,[22] our patients treated with BoTx injection had a smaller reduction in esophageal diameter than patients who had myotomy. Esophageal diameter is also a good indicator of an improved bolus-passage through the cardia: though LES resting pressure decreased in both groups, most of the patients who had BoTx injections still had a nadir LES pressure higher than the upper limit for the normal population and this might result in an obstacle to the passage of food and in an increased esophageal diameter.

Many questions raised by the use of BoTx in achalasia remain unanswered, however: 60% of the patients remain asymptomatic after 1 year, indicating that BoTx may still be effective. Such a period of toxin activity is much longer than in the striated muscle, where the effect of BoTx lasts around 3 months. The foregut's neural network differs profoundly from the neuromuscular junction in that it not only has acetylcholine, but also other peptides that interact with neural stimulation and their action is not fully understood. For instance, botulinum toxin may also have an inhibitory effect on fibers other than the cholinergic ones, or inhibit sensory neurons too, thus explaining the lasting symptom control. Certainly, this fascinating toxin and its use in foregut motor disorders deserve further investigation.

In conclusion, laparoscopic myotomy is safe, offering better dysphagia control, a greater reduction in symptom scores and esophageal obstruction (as measured by manometry and barium swallow) than BoTx. BoTx injection should be recommended to patients unfit for surgery or as a bridge to more effective therapies such as myotomy or endoscopic dilation. The results of the present study also and those of 2 small clinical trials comparing BoTx and esophageal pneumatic dilation,[22,28] suggest that future clinical trials on achalasia should focus on the comparison between pneumatic dilations and laparoscopic myotomy.

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