

Endoscopic polymer injection and endoluminal plication in treatment of gastroesophageal reflux disease: evaluation of long-term results



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ABSTRACT

Background and study aims Use of proton pump inhibitors (PPIs) has made endoscopic treatment of gastroesophageal reflux disease (GERD) more efficient, with reduction in morbidity and complications. However, some patients persist with symptoms despite medical treatment and some are not compliant with it or cannot afford it for financial reasons, and thus they require non-pharmacological

therapeutic options such as surgical fundoplication. Surgery may be effective in the short term, but there is related morbidity and concern about its long-term efficacy. The possibility of minimally invasive endoluminal surgeries has resulted in interest in and development of newly endoscopic devices. Good short-term results with surgical fundoplication lack of studies of is with long follow-up justify our interest in this study. The aim of this study was to investigate the efficacy of endoscopic polymer injection and endoluminal full-thickness plication in the long-term control of GERD.

Patients and methods Forty-seven patients with GERD who underwent an endoscopic procedure were followed up for 60 months and evaluated for total response (RT), partial response (RP) and no response (SR) to endoscopic treatment with reintroduction of PPIs.

Results Twenty-one patients received polymer injection (G0) and 26 endoluminal plication (G1). The number of patients with no response to endoscopic treatment with reintroduction of PPIs increased in time for both techniques (G0 $P=0.006$; G1 $P<0.001$). There was symptomatic improvement up to 12 months, with progressive loss of this trending up to 60 months in G0 and G1 ($P<0.001$). Health-related quality of life score (GERD-HRQL) demonstrated TR in G0 and G1 at 1, 3, 6 and 12 months. The 60-month analysis showed an increased number of patients with SR in both groups. The quality of life assessment (SF-36) showed benefit in G0 up to 3 months. G0 showed a higher rate of complications. There were no deaths. There was healing of esophagitis at 3 months in 45% of patients in G0 and 40% in G1. There was no improvement in manometric or pH findings.

Conclusion Endoscopic therapies were ineffective in controlling GERD in the long term.

Introduction

Gastroesophageal reflux disease (GERD) is defined as a chronic condition characterized by backward flow (reflux) of gastroduodenal content into the esophagus and adjacent organs, re-

sulting in a variable spectrum of symptoms. In recent decades, prevalence of GERD has been increasing in the Western adult population. It is estimated that up to 28% of adults have weekly symptoms of retrosternal burning and acid regurgitation [1]. In

Brazil, close to 12% of the population is affected by this disease. Not surprisingly, GERD is the most common reason for outpatient appointments and indication for upper endoscopy [2].

Proton pump inhibitors (PPIs) in conjunction with lifestyle modifications continues to be the primary therapy for GERD. However, the effectiveness of this intervention is often hampered by adherence, costs, and risks associated with long-term use of PPIs. Anti-reflux surgery is an option for patients with refractory symptoms or in those in whom medical therapy is contraindicated or undesirable [3–7]. Surgical treatment, although effective in the short term, may be associated with non-negligible morbidities, and there is a growing concern about late recurrence [8]. For this reason, there has been increasing interest in alternative treatments that may potentially offer similar results and be associated with faster recovery.

With the development of new technologies, different forms of minimally invasive treatment have been described, aiming to interfere with the mechanism of GERD: injection of polymers (Enteryx, Durasphere, among others), prosthesis (Gatekeeper), endoluminal suture (EndoCinch, Plicator, Wilson-Cook ESD, Syntheon Anti-Reflux Device, His-Wiz Anti-Reflux Device, Medigus SRS; Esophyx), and thermal fibrosis induction by radiofrequency (Stretta radiofrequency ablation).

Immediate results from these minimally invasive procedures and absence of studies with late follow-up periods motivated this study, which aimed to investigate efficacy of two endoscopic techniques – polymer injection and endoluminal full-thickness plication – in long-term GERD control, up to 60 months.

Patients and methods

This study was approved by the Ethics Committee for Analysis of Research Projects (Protocol No. 945/01 and No. 326/03). Reference study number: 1.481.669. The procedures were carried out in the period between February 11, 2003 and July 5, 2005. This study was originally set to a 1-year patient follow-up, during which subjects were followed prospectively by protocol in a non-randomized fashion. It was not the initial intention of the study to follow patients on an annual basis, but after patient voluntary return over the years and given promising results at 1 year, we decided to assess long-term outcomes. Ten years after the initial study, follow-up information was retrospectively reviewed for up to 5 years. This extension in time caused almost a 50% loss in patient follow-up. Many of the patients were lost to follow-up for various reasons, such as a change of address, death due to other causes and unknown.

Inclusion criteria

Patients were included in the study if they were aged ≥ 18 years and had GERD with a history of heartburn for more than 6 months, significant symptom relief $>50\%$ with antisecretory therapy consisting of PPI, esophageal manometry (performed in the last 6 months) showed a resting lower esophageal sphincter pressure (LESP) ≥ 5 mmHg, prolonged esophageal pH-metry (performed in the last 6 months) demonstrated pathological reflux, defined when the total percentage of the

pH time less than 4 is \geq to 4.5% or a DeMeester score >14.7 and agreed to participate in the study with signed informed consent [9, 10].

Exclusion criteria

Patients were excluded from the study if they were pregnant, had a hiatal hernia >2 cm, persistent dysphagia, weight loss, esophageal bleeding, Los Angeles classification grade C or D esophagitis, Barrett's esophagus, any medical condition that impeded the end of the study, coagulopathy or chronically used anticoagulants, had pathological changes in connective tissue that could prevent the secure fixation of the endoscopic plication implant, esophageal or gastric varices, megaesophagus, scleroderma, or esophageal strictures.

Endoscopic procedures were performed with prophylactic antibiotic therapy (cephalosporin 1 g) and sedation according to American Society of Gastrointestinal Endoscopy (ASGE) guidelines [11]. Endoscopic equipment used was a standard videogastroscope (Olympus Optical Inc. model GIF-160).

Description of endoscopic devices for GERD

Polymer injection

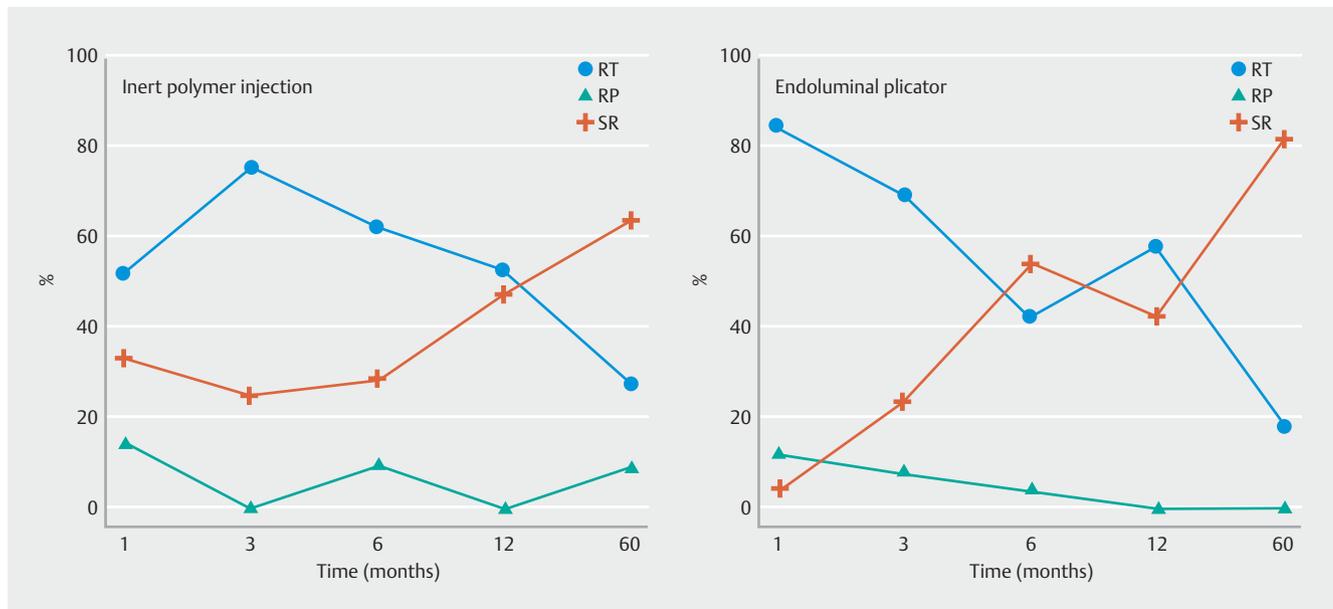
Enteryx (Boston Scientific, Natick, Massachusetts, United States) is an inert alcohol-vinyl-ethylene-based polymer dissolved in dimethyl sulfoxide (DMSO), which is a liquid that when in contact with water forms a solid, spongy, inert and biocompatible mass. To this solution is added radiopaque radiological contrast medium, called tantalum [12]. Polymer injection is performed with a 4-mm catheter previously rinsed with DMSO and filled with Enteryx. The application is performed between 1 and 3 mm proximal to the squamous-columnar junction within the musculature of the cardia, with 1-mL syringes filled with Enteryx under simultaneous fluoroscopic and endoscopic observation. The needle remains in place for 30 seconds and then is removed. Injections are made in the four quadrants, each with a volume of 1 to 2 mL, at the same level. During injection, diffusion of the material around the esophagus (ring-like appearance) is observed and implantation of Enteryx is maintained at the same point up to a volume of 3 to 4 mL. The total volume injected does not exceed 10 mL.

Endoscopic plicator device

NDO Plicator (NDO Surgical, Inc., Mansfield, Massachusetts, United States) consists of an endoscopic plicator instrument, tissue-retracting helical catheter and a suture insert. The plicator instrument is composed of a tissue retractor and a set of two needles, which allow passage of the wire through the entire gastric wall thickness and placement of an implant, forming a fold. Plication is performed with one or two implants, depending on the anatomy identified during the procedure [13].

Clinical evaluation and complementary examination

After obtaining the complete clinical and physical examination, the following questionnaires were applied: (1) Visual Analogue Scale (VAS) of severity of discomfort in a typical episode of heartburn, frequency of heartburn and regurgitation, alone



► **Fig.1** Correlation between therapeutic response and use of PPI. RT, total response; RP, partial response; SR, no response.

and together; (2) Health related quality of life with GERD (GERD-HRQL), which uses the manifestation of heartburn intensity, in decubitus position, relationship with meals, change in diet, heartburn-induced sleep disorder, difficulty in swallowing, pain when swallowing and use of the medication affecting the daily activity; (3) Quality of Life in General (SF-36) in health assessment, with analysis of functional capacity, general health, emotional, physical and social aspects, vitality, mental health and pain. Questionnaires 1 and 2 aimed to evaluate the severity of GERD-related symptoms and were applied in the presence and absence of PPI use, with a seven-day interval. It was questioned the type of PPI, dose, frequency, date of onset and interruption.

The schedule of clinical evaluation, complementary examination, and endoscopic procedures were done during the pre-procedure evaluation without the use of PPI, pre-procedure evaluation during the period of use of PPI and, once selected, the endoscopic procedure was performed and the patient contacted after one week. Clinical evaluation, post-procedure questionnaires and post-procedure examinations were performed after 1, 3, 6, 12 and 60 months.

Evaluations parameters

Evaluation parameters included reduction in drug use related to GERD (dose and frequency), reduction in symptoms index through the VAS (VAS evaluates three things: 1. severity of discomfort in a typical episode of heartburn; 2. frequency of heartburn; and 3. frequency of episodes of regurgitation), GERD-HRQL, and responses to the health assessment questionnaire (SF-36) at 1, 3, 6, 12, and 60 months. The evaluation related healing of esophagitis at 3 and 12 months, modification of the manometric study and 24-hour pH-metry of the esophagus at 3, 6 and 12 months. The parameters for response to endoscopic treatment were defined as: total response (RT) = absence

of PPI use, partial response (RP) = 50% reduction in PPI use, and no response (SR) = daily need for PPI.

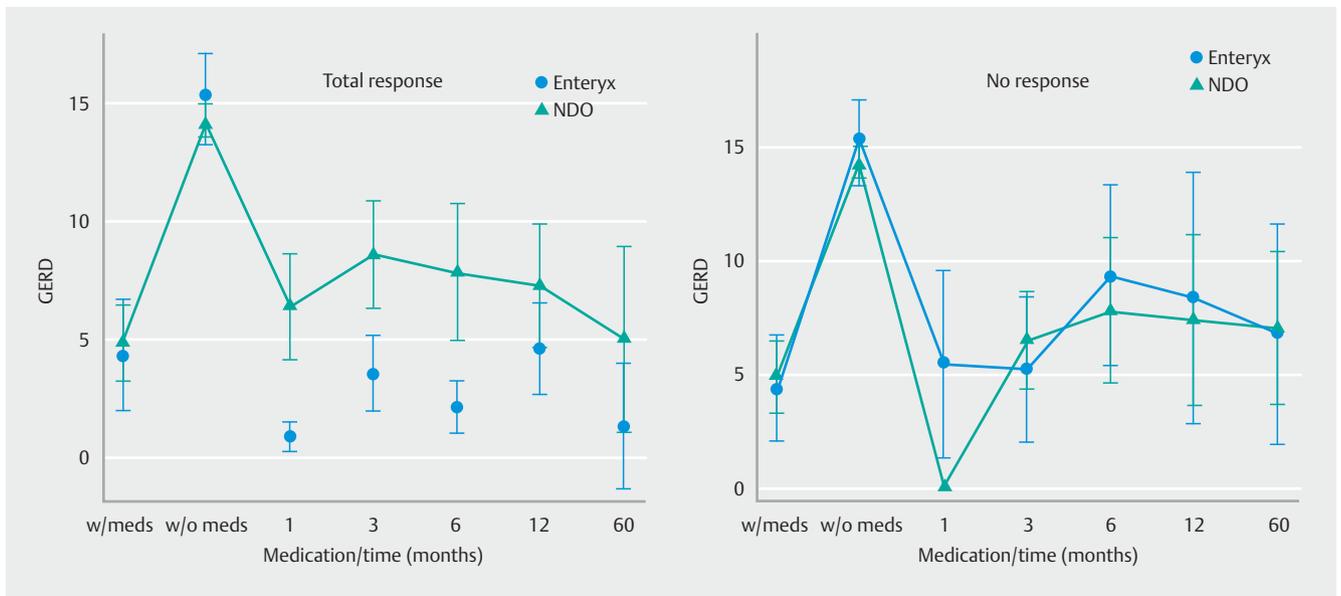
Statistical analysis

The SPSS program for statistical analysis was used. An intention-to-treat analysis was performed. The normality of the data in each period was evaluated through the Kolmogorov-Smirnov (KS) test. For analysis, the ANOVA, Friedman non-parametric test and Mauchly test were used. The level of significance was set at 0.05 ($\alpha = 5\%$). Descriptive levels (P) below this value were considered significant. The paired Wilcoxon test was performed to compare the variables over time with baseline time. Analysis of adverse events was performed using Fisher's Exact Test, which verifies the association between the crossed variables.

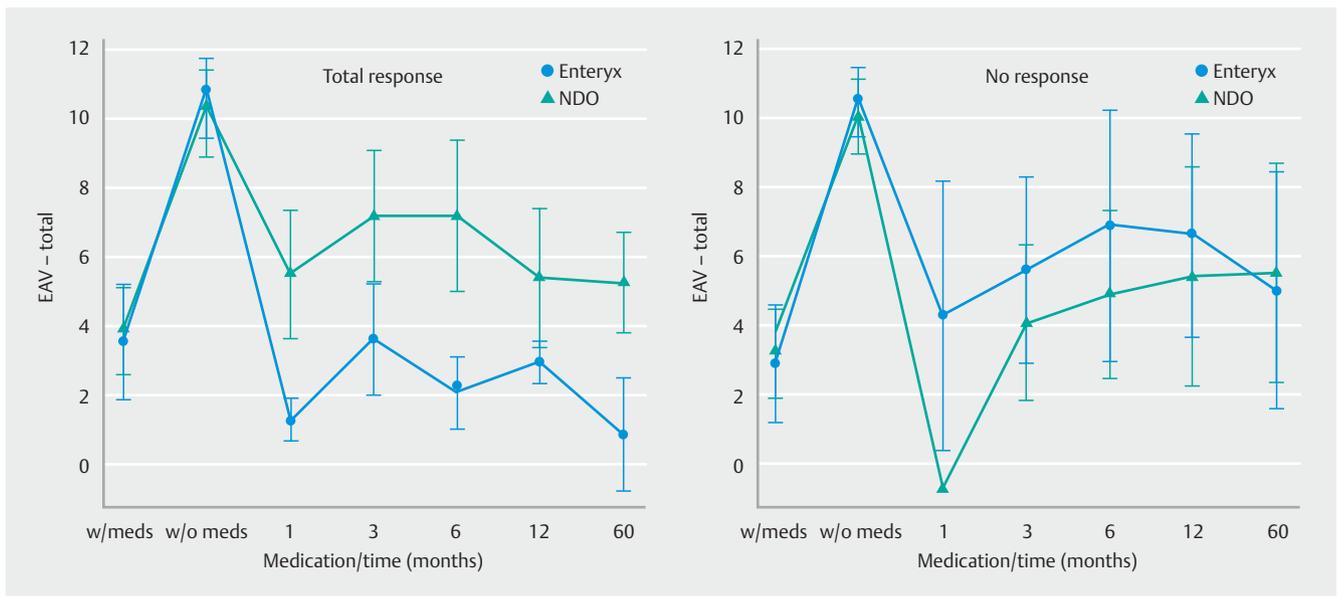
Results

Inert polymer injection (Enteryx) (G0) was performed in 21 patients and endoluminal full-thickness plication (NDO plicator) (G1) was used in 26 patients, and from this group, five received a second endoscopic suture because of failure of treatment at 1 year follow-up. There was a predominance of male patients (12 men, 9 women) in the group submitted to the Enteryx technique, as well in the endoluminal full-thickness plication group (20 men, 6 women), with median ages of 39 (20–70) and 48 (21–69), respectively. The mean time for performing the polymer injection technique was 45 minutes (13 to 60 min) and for the endoluminal full-thickness plication technique was 20 minutes (10 to 59 min).

There was no loss of follow-up in either group for up to 6 months. However, in the polymer injection group, there was a loss to follow-up of 9.6% at 12 months and 47.7% at 60



► **Fig. 2** Analysis of health-related quality of life in patients with GERD (HRQL-GERD). w/meds, with medication; w/o, without medication.



► **Fig. 3** Visual analogue scale (VAS) after intervention in patients with total response and no response. w/meds, with medication; w/o meds, without medication.

months. In the plicator group, there was loss to follow-up of 6.9% in 12 months and 58.7% in 60 months.

► **Fig. 1** shows the correlation between endoscopic therapies and reduction in PPI use. Although there was a trend of increasing patients with no response to treatment from the third month on ($P=0.017$) in the polymer injection group, there is no statistical evidence to prove that no response to treatment increased over time ($P=0.060$). In the plicator group, there was a tendency to increase the frequency of patients with no response to treatment over time ($P<0.001$) (► **Fig. 1**).

According to the analysis by VAS and with respect to the HRQL-GERD, there was a statistically significant improvement

in both groups ($P<0.001$) during the first 12 months. After the 3-month mark, we observed an increase in non-responders in the endoluminal full-thickness plication group and after the 6-month mark in the polymer injection therapy group. After 12 months, there was a significant increase in non-responders in both groups with a greater frequency of regurgitation and need for PPIs. The 60-month analysis demonstrated a significant increase in the number of patients with no response in both groups (► **Fig. 2**, ► **Fig. 3**).

In the analysis of quality of life in general (SF-36), functional capacity improvement was observed in the polymer injection group after 1, 3 and 6 months ($P=0.015$, $P=0.05$, $P=0.04$,

► **Table 1** Post-procedure complications in the polymer injection and endoluminal plication groups.

Complications	Polymer injection		Endoscopic plicator	
	n	%	n	%
Cough	2	9.50	0	0.00
Dyspnea	1	4.80	0	0.00
Fever	4	19.00	0	0.00
Eructation difficulty	8	38.10	0	0.00
Halitosis	7	33.30	0	0.00
Dysphagia	6	28.60	0	0.00
Bloating	2	9.50	0	0.00
Vomit	8	44.70	0	0.00
Regurgitation	2	9.50	0	0.00

respectively). However, in the endoscopic plicator group there was no improvement at any point in time.

There were complications related to the procedure such as fever, abdominal distension, halitosis, dysphagia and vomiting only in the polymer injection group. There were no complications in patients in the plicator group (► **Table 1**).

Three months after the initial intervention, normalization of the endoscopic findings was achieved in 45% of patients who received polymer injection and 40% in the plicator group. In contrast, in the same period, there was worsening of esophagitis in 5% of the polymer injection group and 12% of the plicator group.

At 12 months, we observed complete healing esophagitis in 43% of patients in the polymer injection group and 65% in the plicator group. Pre-procedure findings were maintained in 50% of the patients who received polymer injection and in 30% of the patients who received endoluminal full-thickness plication. On the other hand, we observed worsening of esophagitis in 6% of the polymer injection group and 5% in the plicator group.

The techniques used to increase the length of the lower esophageal sphincter had a significant impact only in the initial 3-month post-procedure control. No benefit was observed in the posterior manometric controls. The techniques employed had no impact on increasing mean respiratory pressure of the lower esophageal sphincter which leads to the conclusion that there was no interference in the motor aspect of the organ.

Considering analysis of the prolonged pH of the esophagus, there was no interference in the acid exposure time and the DeMeester score in the polymer injection group. In the plicator group, there was improvement in the DeMeester score at the initial control of 3 months, which was not maintained over time. There was no interference in control of gastroesophageal reflux with the either technique.

Discussion

Patients with poorly controlled GERD symptoms despite maximal PPI therapy or daily PPI dependence are good candidates for anti-reflux procedures. Long-term PPI use is expensive and has several well-known side effects. Laparoscopic Nissen fundoplication is the surgical “gold standard,” however, endoscopic treatments are minimally invasive and provide prompt recovery [14, 15].

Although different endoscopic techniques can improve reflux symptoms for most patients, short- and long-term efficacy has been variable between the different treatments.

Our initial results with inert polymer injection were encouraging, showing that 71.4% did not require PPIs at the 3-month mark, and 61.9% at 6 months. However, there was a progressive increase in non-responders, observing that 50% did not require PPIs after 12 months and only 27.2% at 60 months. The same conclusion was obtained in the analysis of patients in the endoluminal plication group. In the first month, 84.6% presented total response, in the third month this dropped to 69.2%, in the sixth month to 42.3%, and at 60 months to 16.67%. This study demonstrates the fleeting effect of these therapies.

We can find similar results described in the literature (► **Table 2**). Several prospective observational studies included patients with GERD treated with the NDO plicator. By intention to treat (ITT) analysis, 65% of patients were able to discontinue PPI medications at 6 months [16]. At 12 months, 70% were no longer taking a PPI medication [17]. At 36 months, nearly 60% continued to not require their pretreatment PPI therapy [18].

In contrast to our study, another clinical trial that assessed long-term efficacy of the NDO plicator showed that of the subjects who were PPI-dependent prior to treatment, 67% remained off daily PPI therapy at 60 months [19].

A randomized NDO plicator sham-controlled trial at 3-month analysis demonstrated that the proportion of patients achieving complete cessation of PPI therapy was significantly higher in the NDO-treated group [20].

Another randomized clinical trial directly compared two endoscopic anti-GERD techniques: The EndoCinch and the Enteryx. At the 6-month analysis, PPI therapy could be stopped or the dosage reduced by $\geq 50\%$ in 77% of EndoCinch-treated patients and in 87% of Enteryx-treated patients [21].

In our study, when evaluating the HRQL-GERD scores, we observed a significant improvement in total response to Enteryx therapy up to the 12-month mark ($P=0.002$), but these results were outlived at 60 months ($P=0.250$). The same was observed in the endoluminal full-thickness plication group, where there was an initial improvement in symptoms at 12 months ($P<0.001$), with a progressive increase in non-responders at 60 months.

When analyzing the impact of polymer injection on quality of life score (SF-36), an initial improvement in almost all domains was seen, with progressive loss of response over time. It should be noted that this loss was not so evident because many patients restarted PPIs. There was no improvement in quality of life score (SF-36) in the endoscopic plication group at any point in time.

► **Table 2** Descriptive table of NDO surgical plicator studies.

Author/year	Population	Study type	Control	Efficacy outcome	Follow-up
Pleskow/2004	Chronic GERD > months on PPI	Observational	N/a	Quality of life -GERD-HRQL scores and reduction on PPI medication	6 months
Pleskow/2005	Chronic GERD > months on PPI	Observational	N/a	Quality of life -GERD-HRQL scores and reduction on PPI medication	12 months
Pleskow/2007	Chronic GERD > months on PPI	Observational	N/a	Quality of life -GERD-HRQL scores and reduction on PPI medication	36 months
Pleskow/2008	Chronic GERD > months on PPI	Observational	N/a	Quality of life -GERD-HRQL scores and reduction on PPI medication	60 months
Rothstein/2006	Chronic GERD > months on PPI	Randomized	Sham	Quality of life -GERD-HRQL scores and reduction on PPI medication	3 months
Kaindlstorfer/2007	Chronic GERD > months on PPI	Randomized	Laparoscopic surgery (Nissen and Toupet)	Quality of life -GERD-HRQL scores and reduction on PPI medication	3 months
Antoniou/2012	Chronic GERD > months on PPI	Randomized	Laparoscopic Fundo-plication	Quality of life -GERD-HRQL scores and reduction on PPI medication	3 months
Domagk/2006	Chronic GERD > months on PPI	Randomized	Enteryx device	Quality of life -GERD-HRQL scores and reduction on PPI medication	6 months

GERD, gastroesophageal reflux disease; GERD-HRQL, gastroesophageal reflux disease health-related quality of life; PPI, proton pump inhibitor

In the literature, it is described that at 6 months post-treatment, HRQL-GERD scores improved significantly. By ITT analysis, 64% of patients achieved a reduction of >50% in GERD-HRQL scores and SF-36 scores improved significantly [16]. At 12 months, median GERD-HRQL scores were significantly improved compared with baseline off medication and baseline on medication [17].

Another study assessed efficacy of endoscopic plication, providing evidence of a reduction in GERD symptoms subjects up to 36 and 60 months post-treatment. [18, 19].

A randomized NDO plicator sham-controlled trial at 3-month analysis demonstrated that the proportion of patients achieving >50% improvement in GERD-HRQL score was significantly higher in the NDO-treated group [20].

The two randomized controlled trials of NDO surgical plicator vs laparoscopic-assisted anti-reflux surgery (LARS) for GERD showed similar improvements in GERD-HRQL scores in both groups at 3-month analysis. The LARS group was more effective in controlling heartburn and regurgitation symptoms compared to the NDO plicator [22, 23].

In addition, there was no long-term benefit for the therapies in an analysis with more objective parameters such as endoscopic healing, manometric studies and prolonged pH-metry. Analysis of our results, compared with the literature, clearly shows that there is no relation between normalization of subsidiary exams and improvement or worsening of clinical manifestations.

Only four patients from the entire study underwent LARS at our institution, two patients from polymer injection group and two from the NDO plication group. These operations presented greater technical difficulty and duration of surgery was prolonged. One patient in the NDO plicator group had compromised diaphragmatic pillars, pleura and pericardium.

The rate of complications was comparable to others studies in the literature. Serious adverse events with the NDO surgical plicator included dyspnea after placement of the overtube in two subjects, one pneumothorax, one pneumoperitoneum and one gastric perforation. These patients were treated clinically and with complete resolution, without sequelae. The device was modified after this original experience and no longer requires use of an overtube, and no trauma has been noted subsequently [17].

The Enteryx device was an early option that was ultimately recalled in 2005 following reports of 11 severe adverse events in which the injection procedure resulted in esophageal perforation and 1 death because of aortic puncture.

Absence of severe complications observed with Enteryx injection in this study is probably due to the technical modification employed, in which the LES-ring was obtained after injection of multiple aliquots of 1 mL, in contrast to techniques described in other studies, in which the ring was obtained by single injection or even two punches with large volumes of 10 mL. Considering that the thickness of the organ wall at the level of the esophagogastric junction is up to 5 mm, it is possible that such complications occurred in response to the correlation between volume injected, accommodation capacity and ischemia, as well as by transfixation of the organ wall and injection in an inappropriate place.

There is a clear limitation in the analysis of most of the published studies due to multiple factors, such as lack of uniform objective data and of endoscopic, manometric and long-term pH-metry evaluation. Some parameters evaluated are subjective, such as symptomatology related to use of PPIs. These results may not reflect the reality of the study and the placebo factor should be considered. For that reason, it is necessary to

include a control group although a sham study or placebo would also be valid.

Considering the analysis of systematic reviews [24, 25] and our results, there is insufficient evidence to support use of these therapies in routine practice. Based on our personal experience, compared with the vast literature, we do not recommend adoption of these techniques for GERD therapy.

Conclusion

This study demonstrated that polymer injection and endoluminal plication therapies are ineffective in controlling GERD in the long term.

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Competing interests

None

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