REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Title:
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DOI: 10.17235/reed.2020.7648/2020
Link: PubMed (Epub ahead of print)

Please cite this article as:
Ruiz de León San Juan Antonio, Pérez de la Serna Bueno Julio, Sevilla Mantilla María Concepción, Esteban López-Jamar José Miguel, Sánchez Pernaute Andrés. GASTRO-ESOPHAGEAL REFLUX DISEASE: LIMITS OF MEDICAL TREATMENT AND SURGICAL INDICATIONS. Rev Esp Enferm Dig 2020. doi: 10.17235/reed.2020.7648/2020.

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REV 7648

GASTRO-ESOPHAGEAL REFLUX DISEASE: LIMITS OF MEDICAL TREATMENT AND SURGICAL INDICATIONS.

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ABSTRACT

Background

Proton pump inhibitors have long been considered the ideal treatment for gastroesophageal reflux disease, their limitations and side effects have revealed the need for new therapeutic approaches. At the moment, the therapeutic gains achieved are relatively small or are limited to groups of patients with specific characteristics. This article updates the contributions, indications, and limitations of pharmacological, endoscopic, and surgical treatments.

INTRODUCTION

There are a wide variety of therapeutic options to treat the different forms of presentation of gastroesophageal reflux disease (GERD) (Table 1). The purpose of this article is to update the indications and limitations of these measures.

LIFESTYLE MODIFICATIONS

Lifestyle modifications are part of the usual initial measures (Table 2). They are especially useful in patients with mild and intermittent symptoms. The limited scientific evidence in this area indicates that only elevation of the head of the bed and weight loss are associated with improvement in symptoms in case-control studies (1,2).

PHARMACOLOGICAL TREATMENT

Antacids and Alginate

Antacids are fast-acting, short-lived compounds that neutralize acid and reduce pepsin activity. They provide rapid short-term relief but are not effective in healing erosive esophagitis (EE) (3). They may interfere with the absorption of other drugs (tetracycline, digoxin...).

Absorbable antacids have more systemic side effects (alkalosis), so they should be used for short periods. Non-absorbable antacids, depending on their composition, may cause: diarrhoea, constipation or depletion of phosphates among other unwanted effects, and should be used with caution in patients with renal insufficiency (3-4).

Alginate interacts with acid forming a pH neutral barrier 'raft' floating on top of the ingested chyme that co-localizes in the region of the acid pocket. Combined with an antacid rapidly reduces symptoms and damage caused by acidic and non-acid reflux components, such as pepsin and bile acids (5). Its benefits are scarce in GERD. It is considered as an alternative treatment in non-erosive gastroesophageal reflux disease (NERD), and complementary in patients with GERD refractory to PPIs (6).

Mucosal protective agents

These compounds generate a protective layer of esophageal mucosa and/or strengthen their defense mechanisms.

Sucralfate (sucrose sulfate and aluminum hydroxide) binds to proteins selectively in erosive lesions, facilitating their healing (7). It is effective in the improvement of symptoms in patients with reflux esophagitis (8). His role in NERD is not well determined. It is generally considered as a complementary therapy.

It is not recommended in patients < 14 years, nor in patients with severely altered renal function. Experimental animal studies do not suggest harmful effects on pregnancy (9). It can decrease the absorption of a wide group of drugs.

The association of hyaluronic acid, chondroitin sulfate and poloxamer 407 has a mechanism of action similar to that described for sucralfate. It is more effective than placebo, even in patients with persistent symptoms despite PPI treatment (10), although without proven scientific evidence.

Experience with drugs directly aimed at increasing mucosal barrier resistance such as irsogladine or rebapimide is scarce, with wide variability and generally limited to symptomatic improvement (11-12).

Transient LES relaxation (TLESR) inhibitors

TLESR are the main cause of reflux in normal subjects and in patients with mild GERD. They play an important role in the development of GERD. TLESR inhibitors are indicated in patients with persistent regurgitation despite appropriate antisecretory treatment (13). Of the different groups of drugs investigated, only GABA B receptor agonists and mGluR5 have reached the stage of clinical use (14).

Baclofen is the most emblematic representative of GABA B agonists; its neurological side effects limited its use and promoted the development of other molecules such as Lesogaberan and Arbaclofen placarbil, with little therapeutic gain (13). This, along with side effects, have stopped its development.

Metabotropic receptors of glutamate subtype 5 act at peripheral and central level decreasing vagus-vagal reflex. The most studied drugs are mGluR5 ADX 10059 and AZD2066. Available data from clinical trials are limited. The effectiveness in controlling TLESR of ADX 10059 is overshadowed by the presence of side effects, and the efficacy and safety of AZD2066 needs more research (4).

Promotility agents

One of the most attractive therapeutic targets is that aimed at correcting or improving some of the most important factors related to GERD: LES hypotension, poor esophageal clearance and delayed gastric emptying. Multiple drugs have been investigated including: Selective dopamine receptor antagonists, selective 5-HT4 receptor agonists, muscarinic agonists and even an antibiotic of the macrolide group, erythromycin. Its effectiveness in the esophagus is low and its clinical use is conditioned by the side effects that have led to the withdrawal of some drugs such as cisapride. Its use is relegated to patients with symptoms related to regurgitations and delay of gastric emptying (15).

Inhibitors of acid secretion

The two most important groups of gastric acid secretion inhibitors are histamine H2 receptor antagonists (H2RAs), and proton pump inhibitors (PPIs).

H2Ras (cimetidine, ranitidine*, famotidine, nizatidine and roxatidine) decrease gastric *acid* secretion by reversibly binding to histamine H2 receptors located on gastric parietal cells. Are more effective than placebo at relieving GERD symptoms (16) but are ineffective in healing esophagitis (18). They are indicated in patients with mild GERD and PPI intolerance. The addition of bedtime H2RAs as complementary therapy to PPIs is clinically effective in controlling nocturnal acid breakthrough and GERD symptoms, but patients develop tolerance after weeks or months. Side effects are rare (approximately 4%) (17). The increase in the standard dose has shown no benefit (16).

PPIs block acid production by irreversibly inhibiting the H+/K+ /ATPasa pump (proton pump) on the gastric parietal cells surface. Because of their high power of acid secretion inhibition, they are recommended as a first-line treatment in patients with GERD and other acid-related diseases.

The U.S. Food and Drug Administration (FDA) has approved six subtypes of PPIs: omeprazole, lansoprazole, pantoprazole, rabeprazole and the stereoisomeric compounds esomeprazole and dexlansoprazole. Although its basic structure is similar, in a small number of patients, metabolic pathways and genetic variation in CYP2C19 cause differences in inhibitory activity (18). In most cases these differences are minimal in clinical response and healing of lesions.

They should be taken 30 minutes before the first meal of the day and if necessary, a second dose will be taken before dinner (19). PPIs are well tolerated with few adverse events and no significant differences between them. However, despite its excellent safety profile, there is a growing concern about its overuse and the numerous adverse events published. Most of these relate to prolonged inhibition of acid secretion, pharmacological interactions, or idiosyncrasy or hypersensitivity reactions and are based on observational and retrospective studies, with low evidence and with few consistent data demonstrating causal link. They are sometimes contradictory and many of these alterations have not been confirmed with prospective clinical trials (Table 3) (20,21).

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MEDICAL TREATMENT OF GERD IN DIFFERENT SITUATIONS.

Erosive GERD (EE) /non-erosive (NERD)

Healing of esophagitis is directly related to time to a pH>4 and the duration of treatment. Healing rates with PPIs range from 87.7% to 95.4% (22).

Although patients with EE or Barrett's esophagus have a longer acidic and weakly acidic exposure time of the distal esophagus than NERD patients (23), the intensity of symptoms and response to treatment is similar (24), therefore no differences are established on the initial treatment.

Barrett's Esophagus (BE)

The use of PPIs in BE is recommended in all clinical guidelines (25). Recommendations are made on the need to maintain treatment on a chronic basis and provide for different situations in relation to the presence or absence of different degrees of dysplasia or esophageal adenocarcinoma (EAC). It is recommended to increase the dose if necessary, repeating endoscopy in 3-6 months and, depending on the results, perform endoscopic ablation or surgery. Monitoring of reflux, both before and after endoscopic ablation (26) is advisable since a greater response to radiofrequency ablation has been described when effective pHmetric control is achieved (27). In some cases, it may be helpful to add bile salt chelators and prokinetics.

Although a lower risk of dysplasia/EAC has been observed with the use of aspirin, NSAIDs and statins in association with double doses of PPIs (28), their routine use (25) is not recommended given the low risk of progression of non-dysplastic BE and the possible side effects of these drugs.

Extraesophageal manifestations of GERD (EGERD)

The EGERD manifestations with an accepted relationship with GERD are cough, laryngopharyngeal reflux, asthma, and chest pain. They always require an investigation of other causes. A better response to anti-reflux treatment is obtained in patients who present with typical symptoms, a pathological acid/weakly acid exposure in the esophagus or there is a positive symptomatic association (29). Treatment with double

doses of PPIs and lifestyle modifications is recommended for 3-6 months, as EGERD symptoms take longer to improve than typical GERD. If symptoms persist despite treatment it is advisable to perform a 24-hour impedance-pHmetry on-treatment. If the result remains positive for reflux or there is a positive symptomatic association, anti-reflux surgery should be considered.

Maintenance therapy

Given the high frequency of clinical recurrence in both EE (about 100%) and NERD (≈ 75%) (30,31) and the likelihood of progression from NERD to EE (32), it is recommended maintenance therapy with the minimum dose of PPIs that control symptoms and avoids lesions (33).

Refractory GERD

A patient is considered refractory to PPI treatment when symptoms or lesions persist after 12 weeks on double dose of PPIs. In patients with persistence of symptoms with a single dose of PPIs doubling the dose is recommended (33, 34). If improvement is not achieved it is advisable to rethink the diagnosis by assessing other diagnostic possibilities: therapeutic non-compliance, hypersensitive esophagus, large hiatal hernias, hypersecretion states (Zollinger-Ellison syndrome) and check for reflux (pHmetry-Impedance on- or off- treatment, depending on the case). If refractory reflux is confirmed, then endoscopic or surgical treatment should be evaluated.

ENDOSCOPIC TREATMENT OF GERD

In the last 20 years, various endoscopic techniques have been developed for the treatment of GERD (Table 4). Techniques based on the submucosal injection of different substances into the esophago-gastric junction (EGJ) and some sutures such as EndoCinch or NDO Plicator have been abandoned due to complications and/or poor efficacy. Other techniques are in the early stages of development. At present the possibilities of endoscopic treatment are:

1) Induction of fibrosis at the EGJ. The main representative is the Stretta © device, approved by the FDA in 2000. This catheter is inserted over a guide, fixing the distal

end in the EGJ previously located by endoscopy. The inflation of the balloon at its tip causes the deployment of small needles that are inserted into the muscle layer and, by means of a pedal, energy is released that causes increases in temperature of 65-85ºC. The procedure begins 1 cm above the EGJ and extends to the entire LES and the gastric cardia. The objective is to increase resistance by decreasing compliance and increasing the thickness of the LES (35).

As in most publications on endoscopic procedures, results are highly variable. Some meta-analysis shows significant improvement in both acid exposure and PPI suppression, while other studies do not improve any of this data (36.37). Follow-up reports of 8 and 10 years indicate the maintenance of a statistically significant improvement in the quality of life and up to 41% of patients free of PPIs (38). Complications and adverse events are mild, although some serious events have been reported (38).

2) Endoscopic plication systems: The most developed devices are the TIF (trans-oral incisionless fundoplication) with the EsophyX© system, and the MUSE© (Medigus, TelAviv).

The TIF technique was approved by the FDA in 2007. The EsophyX TIF 2.0 procedure is currently used. It consists of performing a fundoplication that resembles the laparoscopic one. It is performed under direct vision, using polypropylene plates for suturing. There are several studies with this system: - RESPECT, comparing EsophyX 2.0 and placebo against sham maneuver and PPIs, shows a significant improvement of symptoms in the fundoplication group (39.42); - TEMPO, that randomly compares patients treated with TIF and those treated with high doses of PPIs (40) concludes that TIF is more effective at 6 months than PPIs at maximum doses to eliminate symptoms of regurgitation and extraesophageal. In the 5-year result of 44 patients (41), 86% had no regurgitation, 80% improved atypical symptoms and 66% had abandoned daily use of PPIs. A meta-analysis (42) comparing the efficacy of TIF or laparoscopic fundoplication (LF) versus placebo or use of IBPs in patients with GERD includes 7 studies with 1,128 patients. The authors conclude that LF is the technique that further improves LES pressure and decreases % of time with pH<4, while TIF achieved the largest increase in quality of life. TIF is considered a relatively safe technique with few

serious complications (42).

The MUSE plication was approved by the FDA in 2014. It consists of the creation of a previous partial fundoplication using a modified endoscope with ultrasound and a stapler, which allows the placement of 2 or 3 plates each with 5 titanium staples. Results have been published at 6 months and annually over 4 years of 37 patients evaluating efficacy and safety (43). The proportion of patients who remained without PPIs was 83.8% at 6 months and 69.4% at 4 years. The comparison between TIF and MUSE shows similar results at 6 to 12 months in complication rates, subsequent requirement for anti-reflux surgery, and reduction or abandonment of PPIs (44).

3)- Mucosectomy / anti-reflux ablation systems:

They are known by the acronyms ARMS (anti-reflux mucosectomy) or ARMA (anti-reflux mucosal ablation). Both procedures have been described by H. Inoue. In 2014, the results of ARMS in the gastric side of the cardia were published in 10 patients with refractory GERD using the cap system after submucosal injection (45). An improvement in symptoms was described with a significant reduction of % of time at pH<4. All patients discontinued PPIs; 2 patients needed endoscopic dilation by stenosis. The same group has recently published its experience in 12 patients with refractory GERD (46), performing a gastric mucosal ablation by subcardial retrovision and using spray coagulation with a catheter. At 9 months, they refer a significant improvement in symptoms and DeMeester's score. They had no complications and point out that this technique applies to patients who require PPIs following other techniques such as ARMS.

SURGICAL TREATMENT

Surgical treatment is, in selected groups of patients, a good alternative to medical treatment. Its effectiveness is similar and in some cases superior to short- and long-term drug treatment (47). The most common indications for surgical treatment are shown in Table 5.

Laparoscopic fundoplication, with their different variants: the 360º fundoplication or Nissen technique, the 270º partial posterior fundoplication or Toupet technique, and the 180º anterior fundoplication or Dor technique, are the most used procedures. The

objectives of these techniques are to achieve at least 3 cm of intra-abdominal esophagus, repair the diaphragmatic hiatus, and perform a valve mechanism. The Dor fundoplication, due to its lower anti-reflux power, is reserved for the treatment of motor disorders after esophageal myotomy.

The Nissen fundoplication is the reference anti-reflux technique. It achieves reflux control in approximately 90% of patients. Its most frequent side effects are temporary dysphagia and air trapping.

In the Toupet technique, the plication with the gastric fundus only surrounds the posterior 3/4 parts of the abdominal esophagus. The results are similar to those of the Nissen technique, and since the closure of the plication is not complete, the symptoms caused by air trapping are reduced. Although most surgeons consider the Nissen technique to be the most effective, no randomized study has been able to show that it is superior to Toupet's (48).

In the long term, the failure of the fundoplication is estimated between 5 and 20%. Among the most common complications is plication herniation, which generally results in dysphagia, chest pain, and recurrence of reflux. Reoperation for previous failure is more difficult than the first surgery, postoperative complications are more frequent, and the efficacy in controlling reflux is lower.

Reoperation is only recommended in patients with recurrent erosive esophagitis and/or highly symptomatic with marked deterioration in their quality of life due to severe reflux or distal obstruction to the passage of the bolus. The surgeon who performs them must be experienced in anti-reflux surgery, reoperations, and gastric and esophageal resections. Although the recommended approach is laparoscopic, conversion to open surgery is possible.

Reinterventions may require procedures such as mesh hiatoplasty to reinforce the closure of the diaphragmatic crura, relaxation incisions in the diaphragm, and esophageal elongation by tubulizing the proximal stomach to make a "new abdominal esophagus" (Collis gastroplasty). In multioperated patients with refractory reflux or severe esophageal motility disorders, duodenal diversion or, currently, gastric bypass, may be the definitive solution.

New alternatives

Two systems have been presented in recent years as an alternative to traditional laparoscopic fundoplication. The objective of both is to maintain the anatomy of the gastroesophageal junction and to try exclusively to increase LES pressure.

The LINX system is based on the placement around the gastroesophageal junction of a flexible ring of beads with a magnetic core, linked by a titanium thread. The magnets help keep the LES closed. During food intake, the force of the peristaltic waves and the relaxation of the LES cause the magnets to separate, facilitating the passage of the bolus. It was approved by the FDA in 2012. The technique is performed laparoscopically. In patients with a hiatal hernia> 3 cm, the closure of the diaphragmatic pillars is associated, so the difference with fundoplication is the absence of fundic mobilization. It has a good safety profile and has been shown to be effective in controlling symptoms and esophageal pH in selected patients (typical symptoms, with response to PPI, hiatal hernia <3 cm, absence of severe esophagitis). Good results have been reported at 6 and 12 years, with a reduction of 50% or more in the average daily dose of PPIs in 89.5% of patients (49). In approximately 5.5% of cases, it is necessary to remove the implanted devices. The mean time elapsed between the placement of the LINX and its removal was 863 days (50). MRI compatibility is dependent on the LINX model implanted. In the absence of more randomized studies with a sufficient number of patients and follow-up, it is presented as a good alternative to fundoplication in selected patients.

The EndoStim system is based on electrical stimulation of the LES by inserting two electrodes into the muscle layer of the distal esophagus connected to a pulse generator implanted in the abdominal wall that is controlled by an external programmer. The goal is to increase the sphincter pressure without compromising its relaxation or esophageal peristalsis. Most of the studies at 6 and 12 months report good results in the improvement of the quality of life and the reduction or no need of PPI treatment. It has a good safety profile with little or no dysphagia.

CONCLUSIONS

PPIs have long been considered the ideal treatment for GERD. Limitations discovered in recent years of this group of drugs have revealed the need for new pharmacological, endoscopic, and surgical therapeutic approaches. Currently, therapeutic gains achieved are relatively small or are limited to groups of patients with special characteristics.

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Table 1. Therapeutic options for GERD

1. LIFESTYLE MODIFICATIONS
2. PHARMACOLOGICAL TREATMENT
    1. Antacids / Alginate
    2. Mucosal protectors
    3. Transient LES relaxation (TLESR) inhibitors
    4. Prokinetic agents
    5. Inhibitors of acid secretion
    6. Pain modulators
3. ENDOSCOPIC TREATMENT
    1. Injection/implants
    2. Fibrosis by thermal energy
    3. Suture/staple
    4. Mucosectomy/ablation
4. SURGICAL TREATMENT
    1. Fundoplication
        1. Total (Nissen)
        2. Partial (Toupet, Dor)
    2. New therapeutics
        1. Linx
        2. EndoStim

Table 2. Lifestyle modifications for GERD

- Avoid large meals
- Avoid problematic foods (high fat, citrus, coffee, carbonated beverages, alcoholic beverages, spicy foods, chocolate, onions, carminatives)
- Reduce fluids during meals.
- Avoid bending over or lying down after meals (within 2 to 3 hours)
- Avoid eating before exercise.
- Raise the head of the bed (nocturnal symptoms) *
- Weight loss (overweight)*
- Quit smoking
- Avoid tight clothing
- Avoid as much as possible drugs that can promote reflux (Nitrates, anticholinergics, Theofiline, Calcium channel blockers, bisphosphonates...)

* Measures associated with improvement of GERD symptoms in case/control studies.

Table 3. Potential safety issues associated with ppi use

SAFETY PROBLEM	COMMENTS
MALABSORPTION OF ACID-DEPENDENT NUTRIENTS	Uncertain clinical significance
Iron:	
Iron deficiency anemia	Possible, not confirmed
Calcium:	
Increased hip fractures Osteoporosis	Controversial relationship. Assess prophylaxis in patients with osteoporosis.
Magnesium/Potassium:	
Instability Paresthesias …	Uncommon. Control in patients at risk.

Vitamin B12:	Uncommon
Dementia Megaloblastic anemia	Inconsistent evidence. Control in patients at risk.
INCREASED RISK OF INFECTIONS	Proven relationship with little clinical relevance.
Enteric infections:	Low clinical relevance except in at-risk patients.
Clostridium Difficile	Rare. Important cofactor. Avoid PPIs in patients at risk.
Campilobacter, Salmonella	Controversial association, very low risk.
Bacterial peritonitis	Controversial association, very low risk.
Pneumonia:	Variable and not very significant relationship
Intrahospitalaria	Little significant clinical relevance.
UCI COVID-19	Not proven More studies required
HYPERGASTRINEMIA EFFECTS	Proven relationship with little clinical relevance.
ECL cell hyperplasia Gastric tumors Acid rebound hypersecretion Fundic polyps	Little relevance. Assess in cases with marked hypergastrinemia. Possible increased risk in H pylori patients. Probable confounders. Frequent. Adjust to the lowest effective dose. Proven relationship with little clinical relevance. Follow-up in exceptional cases.
PHARMACOLOGICAL INTERACTIONS	Confirmed relationship with multiple drugs

Reducing absorption Altering your metabolism	Potentially important (HIV protease inhibitors, antifungals...).
IDIOSYNCRASY/HYPERSENSITIVITY REACTIONS	
Anaphylaxis Interstitial nephritis …	Rare, potentially serious. Avoid and/or suppress PPIs in patients with risk factors.
Other Collagenous colitis Cardiac ischemia Chronic kidney disease Cerebral ischemia	Rare. Inconsistent evidence. More studies required

Table 4.

Endoscopic anti-reflux techniques			
Injection or implantation	**Thermal energy fibrosis**	**Suture or stapling**	**Mucosectomy or ablation**
Enteryx	Stretta	EndoCinch	ARMS (anti-reflux mucosectomy)
Gatekeeper		Plicator	ARMA (anti-reflux mucosal ablation)
Durasphere		EsophyX	
Plexiglas		MUSE (Medigus)	
		Other	

Table 5. More common indications for surgical treatment of GERD

- Patients who do not respond to medical treatment.
- Patients who respond well but with early recurrence after stopping medical treatment and reject chronic drug treatment.

- Patients with disease progression requiring high doses of PPIs.
- Complicated GERD (Barrett's esophagus, esophageal ulcer, stenosis, large hiatal hernia)
- Intolerance to drug treatment.
- Extraesophageal symptoms secondary to GERD.