

Updates on Management of GERD Disease

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Abstract

Gastro-esophageal reflux disease is a very common disease. Natural history provides an alternative to wellness and reactivating the disease. The purpose of this article is to review the condition of gastroesophageal reflux disease. The article discusses the diagnostic methods, the clinical presentations and the higher incidence of atypical forms and high reflux symptoms. Many patients are not responding to therapy and those who respond to drugs become dependent on the cure. Medical therapy has some adverse events such as anemia, osteoporosis, and infections. Physiotherapy can be an alternative treatment that offers a temporal benefit.

Surgical therapy is performed with laparoscopy, which is less invasive than open procedure and reduces the time of stay. Endoscopic surgery is devoid of postoperative complications and is easily executable. It can be carried out with one day residency. The article outlines the various endoscopic techniques of recent years and reports scientific studies. From these it appears that the efficacy of endoscopic therapies for the treatment of GERD has not been documented with certainty. So, despite the dream of resolving gastroesophageal reflux with mini-invasive or, even better, endoscopic surgical procedures, the experience of real life teaches us that the medical therapy is effective in most cases and risk free, if the patient is followed closely.

Keywords: Laparoscopic fundoplication; Endoscopic fundoplication; Injection techniques; Implantation techniques; Step up approach; Step down approach

Abbreviations: GERD: Gastro Esophageal Reflux Disease; MII: Multichannel intra-luminal impedance; TIF: Transoral Incisionless Fundoplication procedure; ELF: Endo Luminal Fundoplication; H2 RAS: H2 antagonists or histamine H2-receptor antagonists

Introduction

In this review the Author proposes to remember all the appropriate diagnostic methods for the Gastro Esophageal Reflux Disease (GERD) and the consequent best possible therapies. He lists all possible corrective surgery, signaling that an endoscopic, easy and repeatable surgical technique would be the best solution [1-9]. He, after an excursion of the major scientific works on the subject, recalls the lack of long-term efficacy of endoscopic procedures.

The author concludes by saying that well-run medical therapy is the most practical solution, which is ultimately what Patients prefer [10-15]. Gastroesophageal reflux disease is a very prevalent disease in the "healthy" population [16]. It may have several clinical presentations: dysphagia, cough, rhinitis, burning in the jugular region, chest pain that mimics a heart attack, otitis. The definition of GERD is: "a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications" [17]. The most common symptoms are heartburn, regurgitation, and, sometimes, dysphagia. Extra-esophageal manifestations are bronchospasm, laryngitis and chronic cough.

Other symptoms of GERD include chest pain, globus sensation, odynophagia, nausea, glossitis, burning mouth, otitis, postnasal drip,

sinusitis, dysphonia and headache. For the diagnosis it is preferable to make at least a gastroscopy and also an upper abdominal ultrasound. Response to anti-secretory therapy is not a diagnostic criterion for GERD [18]. For most patients, diagnostic testing is required to confirm the diagnosis of GERD, assess for complications and to rule out other diagnoses.

Differential diagnoses can be: infectious esophagitis (candidiasis), pill esophagitis (Elderly patients in antibiotic therapy), eosinophilic esophagitis (you need a histological examination), peptic ulcer disease (you need a gastroscopy), non-ulcer dyspepsia (need gastroscopy), coronary artery disease (it needs a cardiological evaluation), esophageal motor disorders (a manometry is required). Upper endoscopy is not always required in the presence of typical GERD symptoms of heartburn or regurgitation [19], but, for clinical experience, gastroscopy provides evaluation criteria for mucosal damage and anatomy of the esophagus-gastric junction, useful for treating GERD.

Indications for UGI endoscopy are to rule out complications of GERD and alarm features like dysphagia, odynophagia, gastrointestinal bleeding, anemia, weight loss and recurrent vomiting. If severe erosive esophagitis (LA classification Grade C and D) on initial endoscopy, a follow-up endoscopy in mandatory after a two-month course of PPI therapy to assess healing and rule out Barrett's esophagus.

Another indication for upper endoscopy is the control of Barrett's esophagus. The warning signs are: over 50 years of age, chronic symptoms of GERD (5 years), nighttime reflux symptoms, hiatal gastric hernia, excessive weight and cigarette smoke. If symptoms persist after anti-secretive treatment for thirty or sixty days, a 24 hour pH-impedance test should be performed.

Materials and Method

Diagnostics

Gastroscopy is the first step to rule out anatomical and/or organic pathologies (cancer, esophageal ulcer, Barrett and so on).

A 24 hour pH monitoring is the best method to make diagnosis, to count reflux episodes and to verify that they are related to the symptoms. The data gained from the 24 hour pH monitoring are the total number of reflux episodes (pH=4), the longest episode of reflux, the number of episodes longer than 5 mins, the extent of reflux in upright position and supine position and the correspondence between symptoms and reflux episodes.

A new method for 24-hour esophageal pH-metry without the nose-gastric probe is the Bravo Method. The BRAVO Wireless Receiver is used for storing data from the esophageal pH measurement capsule for a period of 48 hour (in some cases the study may be extended up to 96 hour). The BRAVO capsule is clamped by a positioning catheter during gastroscopy on the esophagus's inner wall, measures and sends the measured pH values to a small receiver attached to the patient's belt. There are 3 buttons on the receiver for the symptoms that the patient can press when he or she complains of pain, regurgitation or burning during the procedure. The patient can also keep a diary to record the meals and the periods of sleep. At the end of the procedure the patient will return the receiver and the data will be downloaded and analyzed to determine the report. The disposable cap will spontaneously collapse and pass through the intestine to be expelled after a few days. The benefits of this study are the absence of the naso-gastric probe, the study in more physiological conditions (however, the presence of a probe may cause alterations in the patient's lifestyle and / or reflux), the possibility of prolonging study up to 96 hour (after 48 hour the patient must still go to the surgery to download the track and then come back a second time to download the one for the next 48 hour) and then to reduce false negatives (patients with reflux disease but studied in a period of well-being). The only limit of this exam is the cost of the appliance, which limits its use.

The Mii-pH-24 hour is the study of the refluxes by the Multichannel intra-luminal impedance (Mii), a catheter-based method to detect intra-luminal bolus movement within the esophagus [20]. Mii is performed in combination with manometry or pH testing. When combined with manometry, it provides information on the functional (ie, bolus transit) component of manometrically detected contractions. When combined with pH testing, it allows for the detection of gastro-esophageal reflux independent of pH (ie, both acid and non-acid reflux).

The esophageal pH-impedance (MII-pH) is today considered the most reliable method (Gold Standard) to objectify gastro-esophageal reflux as it allows to recognize any episode and to define the composition, duration, location and pH. The main indication of this method appears to be the study:

- of patients endoscopically controlled and with symptoms resistant to therapy with proton pump inhibitors;
- of patients with atypical symptoms, such as chest pain or symptoms extra-esophageal (such as bronchial asthma, chronic cough) not otherwise justified;
- of the patients in which it is placed indication to surgical treatment of reflux disease.

Esophageal manometry

Esophageal manometry should be performed to exclude motility disorders, associated with reflux disease, and to evaluate the sphincter apparatus so that the surgeon can decide what type of intervention to perform (Nissen or Toupet or Dor). The method allows to evaluate the mean pressure and the response to swallowing the lower esophageal sphincter. Body of esophagus is assessed for the effectiveness of peristalsis. Normal pressures at LES range from 12 to 30 mm of Hg (millimeters of mercury). Sphincter generally relaxes to the pressure of gastric baseline for several seconds when a swallow is initiated. Ineffective esophageal motility is defined as 70% peristalsis. Distal esophageal amplitudes 30 mm of Hg is associated with significant GERD.

Surgical management

Indications for surgery are the failure of optimal medical management, the noncompliance of the Patient, a high volume reflux, a severe esophagitis by endoscopy, a benign stricture consequent to erosions or ulcers, a Barrett's columnar-lined epithelium (without severe dysplasia or carcinoma), the young age and/or patient choice, considering the adverse events of chronic medical therapy. The aim of the surgery is to bring back the esophagus's sphincter portion at the level of the diaphragm, to create a sort of scarf around the Gastro-Esophageal junction, to prevent it from rising, to reduce hiatal hernia, to close the crural fibers, in order to reduce diaphragmatic flaws, and to correct any associated anatomical anomalies.

Specific anti-reflux surgeries

Belsey Mark IV: This method has been the gold standard before the advent of laparoscopy [21]. It is a partial anterior wrap, though left 5th intercostal space postero-lateral thoracotomy. The fundoplication, according to Belsey Mark IV, is performed using a thoracic approach. After mobilization of the gastric bottom, the stomach is sutured to the esophagus 1 cm above the esophagus-gastric junction, for 270 degrees of esophageal circumference. A second row of sutures is made through the diaphragm, the stomach and the esophagus. When these sutures are completed, the esophago-gastric junction and the tie packaged with the fundoplication are anchored below the diaphragm. The repair of the crural fibers ends up the intervention.

Collis gastroplasty: This method consists in transforming the upper part of the small curve into tube form [22], in continuity with the esophagus. Collis gastroplasty is a surgical procedure performed when the surgeon wants to create a Nissen fundoplication, but the portion of the esophagus lower than the diaphragm is too short. So, there is not enough esophagus to wrap around. A vertical incision is made in the stomach parallel to the left edge of the esophagus. This effectively stretches the esophagus. Stomach fundus can then be wrapped around the new esophagus, thereby reducing the stomach acid reflux in the esophagus. The disadvantages of this procedure are that the neo-distal esophagus does not co-ordinate with peristaltic esophageal waves and the fact that the neo-esophagus mucosa continues the secretion of acid.

Hill procedure: The fundoplication according to Hill is a partial fundoplication that can be performed through a chest or abdominal approach [23]. After mobilization of the bottom of the stomach and the gastro-oesophageal junction, the arcuate medial ligament overlying the aorta is dissected. A serrated suture is performed through the pheno-esophageal ligament and through the median arcuate ligament. Three similar sutures, one top and two lower ones, are packed to

complete the casing. The sutures are tension-linked by the intraoperative manometry. Long-term results of Hill's procedures were favorable, with good and excellent results in 85-90% of patients. However, the need to monitor intraoperatively the pressure of the lower esophageal sphincter and the lack of familiarity with arcuate ligament deterred most surgeons from adding this technique to their surgical armours.

Nissen fundoplication: Fundoplication sec. Nissen consists in mobilization of the gastric fundus, with which it creates a valve, surrounding the esophagus to 360°, in order to recreate the structural condition of operation of the anti-reflux valve, restoring the angle of His [24]. It is obtained a full 360° posterior wrap around the lower 4 cm of esophagus. It can be performed by standard laparoscopic technique. Today, the fundoplication is almost exclusively performed laparoscopically, whereas just a few years ago we performed a laparotomy median umbilical xiphoid and, less frequently, were accessed via the esophagus to the thoracic (ie in the case of severe obesity). Both techniques were very labor-intensive and required very long response times. The spread of laparoscopic surgery has partially changed the attitude and the directions of the reflux surgery. This, above, was indicated only in cases with coexisting hiatal hernia of significant size. Currently, some guidelines suggest the laparoscopic surgical treatment for patients who respond discreetly to medical therapy, but who have severe relapses after withdrawal of the same, or that they are young and do not want to undergo a continuous medical treatment.

Partial fundoplications

Toupet fundoplication is a partial posterior wrap [25]. This technique according to Toupet fundoplication is reserved for cases in which the study preoperative manometry reveal a poor peristaltic function of the esophagus. It packs a plication not 360° (as in the Nissen) but at 270°, creating a gastric sleeve, which surrounds the esophagus only on the rear half.

Fundoplication according to Dor technique. The fundoplication Dor is instead the antireflux technique, in which the gast Diagnostics ric sleeve envelops the esophagus only on the front half [26].

Complications of laparoscopic fundoplication can be [27]:

- **Intra operative:** Intra-operative complications can be the access injuries, a vascular lesion and hollow viscus or solid organ injuries, dissection injuries like stomach, esophagus and vagus nerve, bleeding from aberrant arteries, aorta, vena cava, short gastric arteries.
- **Early post-operative:** Early post-operative complications can be a delayed perforation of stomach and esophagus, deep vein thrombosis, pulmonary complications, dysphagia, early wrap herniation.
- **Delayed post-operative:** Delayed post-operative are dysphagia, poor motility, tight wrap, twisted wrap, gas bloat syndrome, recurrence of reflux, wrap herniation, wrap disruption, incompetent wrap, diarrhea, vagal injury.

The choice of surgery depends of many factors influencing, like the degree of esophageal shortening (Collis procedure should be preferable), disturbances of esophageal motility (Toupet technique would be better), prior operations and local expertise with laparoscopic techniques. For early uncomplicated disease the choice is the trans-abdominal Nissen (laparoscopic if possible) fundoplication. In case of decreased motility, although surgery cannot directly

influence esophageal motility in patients with GERD, surgeon can choose Toupet or Dor procedure. In case of normal length but decreased motility, the complete fundoplication is discouraged; (lap or open) Toupet or Hill or transthoracic Belsey procedure could be performed. In case of shortened esophagus, the Collis (esophageal lengthening) gastroplasty combined with an intra-abdominal or intra-thoracic fundoplication is preferable.

Laparoscopy vs. Open

Laparoscopic approach has a faster convalescent rate (3 fewer days in hospital), a faster return to work (8 days sooner), and a similar treatment outcome [28]. But patients undergoing laparoscopic surgery also has a higher rate of re-operation.

A new surgical procedure, Lynx system: This device is called LINX Reflux Management System [29] and consists of a series of titanium spheres, with a magnetic core inside. This "magnetic collar", as it is called, aims to strengthen the anti-reflux of the lower esophageal sphincter efficacy and is implanted with standard laparoscopic procedure, under general anesthesia. The device is wound and fixed around the sphincter cardia, does not involve any anatomical alteration of the surrounding structures and does not require a post-operative specific diet. The spheres are interconnected, with independent titanium wires, and form a flexible ring, that surrounds the sphincter circularly.

The strength, that the magnetic cores apply on each other, increases the ability of the sphincter to resist opening pressures from below, ie from the gastric. These magnetic bonds are instead broken easily upon arrival of the food bolus from above, that is, originating from the esophagus, which has greater propulsive force, due to the peristalsis and the force of gravity, allowing the free passage of the bolus itself and the subsequent closure sphincter. For proper implant procedure, the device must be sized to the circumference of the patient's esophagus, and different sizes are available (11 to 17 balls). It is necessary, therefore, a preliminary measurement of the circumference to be used, which is made with a second device, the LINX Esophagus Sizing Tool. This surgical method is a recent application and studies are underway to validate its effectiveness. The consequence of the intervention is the inability to perform the radiological examination of magnetic resonance imaging.

Another laparoscopic procedure is the Endostim method: The Endostim is another laparoscopic surgical procedure [30], which does not at all alter the anatomy of the esophagus-gastric sphincter. The surgical procedure, in fact, only serves to implant electrodes in the distal esophagus. The method is named from the implantable pulse generator (IPG), which is called EndoStim II, a stimulator that sends electrical impulses to the lower esophageal sphincter (LES), through two electrodes. The device, which has a lithium battery, is placed under the skin of the abdomen and delivers pulses at the esophageal-gastric sphincter via a connector cable. The electrodes are implanted in the sero-muscular layer of the cardia. The surgery to implant the electrodes and the stimulator lasts 45 mins and is performed under general anesthesia. The indication is for patients with gastro-esophageal reflux disease of mild degree, in the absence of cardiac arrhythmias.

Endoluminal therapies

Radiofrequency (Stretta): This method is based on radiofrequency energy delivery [31]. The equipment is made up of: RF control module

and Flexible Stretta catheter. Catheter is a 20 Fr soft bougie tip and a balloon, which opens into a surrounding basket. 4 electrodes deliver 60 to 300 Joules of RF energy to each needle, heating the surrounding muscle tissue to the target temperature between 650 C° to 850 C°. Stretta procedure is based on the use of a device that releases energy in the form of radio frequency, at cardias level, though needle electrodes inserted in the junctional muscle tissue. This method can be performed with the device in the passage of the endoscope channel or inserting it later, under radiological guidance, after taking the measures during gastroscopy. The procedure is a minimally invasive method. The action takes place in two stages: a gastroscopy is performed to measure the patient's esophagus. Subsequently, orally, placing a catheter, until the lower esophageal sphincter, previously located.

In this point dilates the balloon catheter, from which protrude four needles, with which the radio frequency is applied on the distal esophageal mucosa and cardial junction. The procedure lasts about 30 mins and is performed under general anesthetic, as you need the patient's immobility. The heat should make the lower esophageal sphincter more toned and resistant. Certainly they are compromised the sensory receptors of the esophagus, so you get the reduction of the pain sensitivity. Continuous irrigation of the esophageal mucosa and surface temperature monitoring are utilized to prevent thermal mucosal injury. The transmitted energy intensity can be adjusted based on the symptoms and the sending of the impulse is suspended under clinical judgment of the specialist.

Techniques of endoscopic fundoplication

Bard EndoCinch Endoscopic suturing system: The EndoCinch was the first form of intraluminal gastroplication [32], which has obtained the approval from the FDA in the United States, in 2006. The procedure, which takes its name from the instrument used, consists in capturing, in a niche, which is located in the final part of a special endoscope, part of the mucosa of the esophagogastric junction, where it is sewn to form folds. In this way, it reduces the cardial space, as happens in the surgical intervention (fundoplication procedure), creating these mucosal folds below the lower esophageal sphincter, with the sutures carried through the gastroscopy. This method, as all endoscopic procedures, is burdened by the loss of effectiveness in the long term, not sufficient for the sealing of stitches.

The same method was also used for obese patients, reducing the gastric lumen and putting in communication a gastric pouch, reduced in size, with the small intestine, obtaining an early sense of satiety, and simulating the surgery procedure of "sleeve gastrectomy". Also this procedure presents the same drawback of the failure of the sutures tight. As the procedure with Esophyx, EndoCinch also has the disadvantage of having to be carried out with two tools and the overtube too, which makes the method complicated. The presence of the room, where it is sucked the mucosa of the esophagogastric junction, before applying the stitches, had hoped for a better grip of the same, as compared to other endoluminal procedures. But the clinical evidence does not support this point of view. The procedure is effective in short-term follow-up period and the complication rate was relatively low. Sutures were significantly lost within the 6-month follow-up period, thus necessitating re-procedure in about 25% of the patients.

In a study [33], a total of 70 patients treated with EndoCinch at a single referral centre were studied prospectively. All patients were interviewed using a standardized questionnaire regarding their symptoms and medication prior to and 18 months after EndoCinch. In addition, follow up included endoscopy, 24 hour pH monitoring, and

oesophageal manometry. The procedure was well tolerated without major short-term or long-term complications. Eighteen months after EndoCinch, 56/70 patients (80%) were considered non-responders to treatment as their burning symptoms did not improve or the proton pump inhibitor exceeded 50% of the initial dose. Endoscopy showed all in situ sutures in 12/70 (17%) patients, while no suture was present in 18/70 (26%). In 54 and 50 patients, no significant changes in 24-hour pH monitoring were observed (median pH 4/24 h, 9.1% v 8.5%, p=0.82) or lower esophageal sphincter pressure (LES) (7.7 v 10.3 mm Hg; P=0.051). The mean length of the lower esophageal sphincter was slightly increased (3.0 to 3.2 cm, p 0.05). In conclusion the Endoscopic Gastroplication (EndoCinch) is a safe and minimally invasive endoscopic treatment for GERD with satisfactory short-term results. Instead, the long-term outcome is disappointing, probably due to loss of sutures in most patients. Therefore, technical improvements to ensure suture duration are mandatory before endoscopic fundoplication can evolve as a therapeutic option for the treatment of gastro-oesophageal reflux disease.

Esophyx™ System with Serosa Fuse™ Fastener: They are called TIF (Transoral Incisionless Fundoplication) all endoscopic procedures, performing a fundoplication of the stomach, to the cardia level. The device creates a full-thickness fold, from serosa to serosa, and strengthens the sphincter esophageal-gastric. These procedures are less invasive alternatives of laparoscopy. The Esophyx device [34], for the TIF method, which means Transoral Incisionless Fundoplication, is manufactured by EndoGastric Solution and allows the creation of a fundoplication esophagogastric of 2-3 cm thick, for circumferential extension of 270°, capturing the mucous tissue with 12 or more points of polypropylene suture. The device is used in combination with an endoscope flexible video, which provides the endoscopic visualization throughout the operation. This necessity of double instrument makes complicated the procedure and has meant that the technique has been partly abandoned in favor of a similar procedure, but using a single instrument, which allows the display and simultaneously the operation. The Esophyx proceedings showed, as many authoritative scientific journals have published, a good symptom control, but for a short time, because the intervention does not allow the mobilization of the gastric fundus, the tension on the stitches, causes, in the long run, their failure and the return to the status quo ante. It is known, moreover, that even surgical procedures, in many cases, are beset by recurrent, after years, but sometimes after a few months.

The ELF procedure (Endoluminal Fundoplication) can be tailored to the individual patient and his particular anatomy. The post-intervention histological examinations confirm that Esophyx creates a valve, which incorporates the muscular wall of the fundus of the stomach, made more solid by the development of collagen between the two layers of the fold. The brake-esophageal ligaments are incorporated within the valve, stabilizing and increasing their holding, anchoring it to the diaphragm. Esophyx reduces adverse events, frequent in surgical approach, such as dysphagia, pain and longer recovery times. The long-term studies, however, have dampened enthusiasm, in view of the recurrence of the symptoms of the problem and because of the failure of the stitches. In fact, working endoscopically, it is not possible to release and mobilize the gastric fundus, which, for this reason, it exerts pressure and traction on packed sutures. In the long run, therefore, the esophagogastric junction becomes again pathological.

MUSE (Medigus Ultrasonic Surgical Endostapler): This method, similar to that used with the Esophyx TIF, offers the advantage of the

one tool, equipped with a stapler, Israeli ideation, MUSE [35], in which the presence of a mini-ultrasound on the tip, allows the identification of point exact, where the thickness of the lining of the esophageal-gastric junction is increased, allowing you to capture greater thickness of the mucous layer, safely operating. In other words, the operator runs a smaller risk of transmural mediastinal drilling, because he assesses, with the mini-ultrasound, the wall thickness, and he captures more tissue, making it more stable the stitches.

Endoscopic fundoplication with GERD-X The novelty of platelets:

From a couple of years, though, the new GERD-X system applies the stitches [36], fired from the stapler, which have, at their ends, two plates, of poly-tetra-fluoro-ethylene (PTFE), which reinforce the suture and make it resistant to traction, exercised from the tissues. These platelets, formed of the same material that is used in surgery to pack the wire mesh for hernia protection, cement subsequently with the tissue, making it more stable plication. Studies underway and those already performed, with the previous Plicator of NDO Surg, similar to GERD-X, but not single-use, demonstrate a greater hold over time of endoscopic plication with platelets, comparable to surgical fundoplication. The new Gerd-X tool is disposable and provides that, within it, a thin gastroscope of service passes, for visual control during the intervention. The Operator is facilitated by the excellent maneuverability and by the micro-hydraulic technology, which enables fast and effective movements, with precise closure of the stapler. The retractor of mucosa serves to capture the appropriate amount of tissue, to obtain a full thickness plication, with a technique of suck and shoot, which brings the mucosa inside of the valves, where the points are pre-assembled, with the plates described. At this point we shoot the stapler and this operation is repeated two (or three) times, to obtain a 180° anterior fundoplication.

The procedure begins with the placement of a guide wire, passed inside the operator channel of a gastroscope. On the guide wire is advanced the applicator Gerd-X and, subsequently, a pediatric ultrathin gastroscope is inserted into the channel of the applicator. Both the gastroscope that the Gerd-X are positioned at 180° retroversion. Under visual control of the gastroscope camera, the operator applies the sutures described, operating twice (or three times), in succession, the timing of the method. The retractor of mucosa serves to capture the appropriate amount of tissue. Retractor leads the mucosa inside the valve, where there are the points pre-assembled with the plates described. Clinical studies, to which I refer, show a minimal complication rate (only one case of bleeding, of 37 patients, treated conservatively with endoscopy and blood transfusion). They not occurred organ perforation or post-procedural stenosis. The subsequent checks and the follow-up have shown, with appropriate score, a clear improvement in the quality of life and a reduction of the phenomena of reflux, evaluated with reliefs of Impedance-pH-metry and manometry.

The advantages of the endoluminal endoscopic procedures, compared to surgery, are the reduction of operative complications (perforations, bleeding, post-procedure stenosis), the reduced period of hospitalization, the simplicity of the intervention, with the possibility of repeating, or of switching to surgery, in case of ineffectiveness. In the early 2000s, the full thickness plicator (Ethicon Endosurgery, Sommerville, NJ, USA) was developed for endoscopic treatment of gastroesophageal reflux disease (GERD). The aim was to restructure the anti-reflux barrier by applying intra-gastric lower esophageal sphincter sutures. Studies with this device had involved the placement of a single suture to create the plication. The purpose of a

study [37] was to evaluate the safety and efficacy of 12 months of this procedure using multiple sutures to repair the gastroesophageal junction (GE). It is a multicenter study, prospective in four tertiary centers.

Eligibility criteria were: Symptomatic GERD according to GERD-Health Quality-of-Life Questionnaire (GERD-HQL) without pharmacological therapy and pathological reflux (abnormal pH 24 hour) requiring daily intake of proton pump inhibitor. Patients with Barrett epithelium, esophageal dysmotility, 3 cm hiatal hernia and esophagitis (grade III or above) were excluded. All patients were subjected to a full-thickness endoscopic plication with linear placement of at least two plate sutures in the gastric cardiac region. Twelve months after treatment, 74% of patients showed an improvement in GERD-HQL scores of 50%, with an average decrease of 17.6 points compared to baseline (7.8 vs. 25.4, $p=0.001$). Using a model of intention to treat, 63% of patients had symptomatic improvements of 50%, with a mean decrease of GERD-HQL of 15.0 (11.0 vs. 26.0, $p=0.001$). The need for daily proton pump inhibitor (PPI) therapy has been eliminated in 69% of patients at protocol-based 12-month and 59% intentional basis. Adverse events including post-abdominal pain (44%), shoulder pain (24%) and chest pain (17%). No long-term adverse events occurred. No long-term adverse events occurred. In conclusion the endoscopic full-thickness plication using multiple Plicator implants can be used safely and effectively to improve GERD symptoms and reduce medication use.

Another study [38] compares the efficacy of endoscopic application and laparoscopic fundoplication on quality of life and the control of symptoms. 60 patients with documented reflux disease were randomly assigned to endoscopic or laparoscopic endoscopy. The score of the quality of life and the classification of the symptoms were recorded before treatment, the and twelve months after surgery. The results were verified for the statistical significance set at a p value of 0.05. Twenty-seven patients in the endoscopic group and 27 patients in the surgical group were available for follow-up. Quality of life scores showed a substantial and similar increase for both groups after treatment. The significance was: for retrosternal pyrosis ($p=0.02$), for regurgitation ($p=0.004$) and for asthma ($p=0.03$) in the endoscopic group, while in the laparoscopic fundoplication group it was more effective to control the symptoms of heartburn ($p=0.01$) and regurgitation ($p=0.05$) compared to Endoscopic procedure. In conclusion the endoscopic application and laparoscopic fundoplication resulted in significant improvement in symptoms with similar grade scores in a selected population with gastro-oesophageal reflux disease, while surgical treatment was more effective for heartburn symptoms and regurgitations at the expense of higher rates of short-term dysphagia.

Another five-year multicentre study [39] reports that PPI-dependent subjects before treatment lost 67% (20/30) need of PPI assumption daily at 60-months follow up. Life Quality Scores (HQL) related to the healing of gastro-esophageal reflux disease show a significant improvement over the base with a statistical score (10 versus 19, $p=0.001$). Additionally, 50% (16/32) of subjects got scores above 50% of their quality of life. No adverse events emerged. These results were comparable to the observed 36-month follow-up results. In conclusion, endoscopic application may reduce the symptoms of GERD and the use of drugs for at least five years after the procedure without long-term adverse events after treatment.

Another study [40] was carried out on the basis of data on esophageal manometry and pH impedance measurement, checking these data one year after the full thickness endoscopic plication for the

treatment of gastroesophageal reflux disease by performing multiple sutures with endoscopic plicator. The objective of this study was to evaluate reflux symptoms 12 months after gastroplication using intraluminal multichannel impedance monitoring. This open, prospective, monocentric study was carried out at the Hospital Service Center in Zell am See, Austria. Patients enrolled were those who did not exhibit hiatal gastric hernia, who had atypical symptoms of gastro-oesophageal reflux documented, persistent or recurrent, despite treatment with a proton pump inhibitor. 36 patients were subjected to full thickness endoscopic gastroplication with one or more plicator sutures.

Measurements of quality of life indexes related to gastroenterological disorders and specific for gastro-esophageal reflux have been performed. Improved symptoms score was statistically significant at follow-up ($P < 0.01$). They improved atypical reflux, swelling, dyspepsia. Twenty-five patients returned to follow-up to perform the esophageal manometry and multichannel intraluminal pH-impedance 1 year after the surgery. De Meester scores dropped from 20 to 10 (statistical significance $p = 0.029$). The total number of episodes of proximal reflux episodes, both in orthostatism and in clinostatism, decreased with statistical significance ($P < 0.05$). Manometric data were virtually unchanged. The percentage of Patients taking proton pump inhibitors on a daily basis after the procedure was 11.5%. There was only one adverse event (bleeding) that required surgery and blood transfusion. Three of 36 patients (8.3%) had symptoms persistence and were assigned to fundoplication laparoscopic surgery. Limitation of the study was that there was no randomized comparison between endoscopic procedure and laparoscopic fundoplication and that the follow-up interval was short. In conclusion the endoscopic fundoplication is safe and achieves objective and subjective improvements.

A report of 2009 on clinical policy [41] has revealed that the safety and efficacy of all endoscopic therapies for the treatment of gastro-oesophageal reflux disease have not been established in the medical literature published so far. Studies were generally small in size, without adequate control groups and provided only short-term follow-ups. Further well-designed clinical studies with long-term follow-up are needed to determine if endoscopic therapies benefit from effective results in patients with gastro-oesophageal reflux disease, eliminating symptoms, preventing recurrence or progression of the disease, healing Esophagitis and reducing the need for pharmacological therapy.

Anti-reflux endoscopic technique with "Gatekeeper" methodology

The endoscopic technique for gastro-oesophageal reflux with the Gatekeeper method [42] uses a soft, flexible and expandable prosthesis made of polyacrylonitrile (HYPAN) hydrogels. The prosthesis is implanted in the esophageal submucosa and, over time, the prosthesis absorbs water and expands, creating a mass in the plant region. There are no new studies that bring new evidence about injection techniques and plant techniques for gastro-oesophageal reflux in the latest literature. In a Randomized Controlled Trial (RCT) Fockens et al. evaluated whether the endoscopic implant of an injectable oesophageal prosthesis, the Gatekeeper Reflux Repair System (GK), was a safe and effective therapy for controlling gastro-esophageal reflux disease. The study concluded that the GK procedure was associated with some serious, but uncommon, complications. However, no statistically significant difference had been observed between the treatment group and the control group in a 6-month follow-up.

Method with Plexiglas: Plexiglas (polymethylmethacrylate PMMA) is a procedure for injection of an inert polymeric material in the sub-mucosa of the proximal zone of the lower esophageal sphincter [43] to make the sphincter continent and counteract the transient openings of the cardiac or lower esophageal sphincter (tLESRs). Plexiglas is a suspension of poly-methyl methacrylate microspheres in a gelatin solution. Jelly is phagocytised by macrophages within 3 months and is replaced by fibroblasts and collagen fibers.

Durasphere: Another mass agent that is used for the same reason is the Durasphere, made up of small carbonaceous pyrolytic granules (Durasphere) [43]. This was used to treat gastro-oesophageal reflux disease. Durasphere has been approved by the Food and Drug Administration (FDA) as a mucous urethral bulking agent. The use of this product for oesophageal reflux should be considered as off label.

Enteryx system: The Enteryx is a co-polymer of Ethylene-Vinyl-Alcohol (EVOH) and Tantalum, a radiopaque agent, dissolved in Dimethyl-sulfoxide (DMSO). Method: 6-8 ml of 8% ethylene vinyl alcohol (EVOH) polymer is infused at a rate of 1 ml/min to the muscle or deep submucosal layer, 1-2 mm caudal to the Z-line. Although Enteryx does not affect LES pressure, the distensibility and shape of GE junction is changed. This solution precipitates in the form of an inert mass and reduces the cardiac opening. In 2005, the Food and Drug Administration ordered the immediate suspension of ENTERYX, as had been reports of serious adverse reactions, especially embolization [44].

Chen et al. in a study of 2009 [45] conducted a review that included 33 studies examining 7 endoscopic procedures to treat gastro-oesophageal reflux: STRETTA procedures, Bard EndoCinch, Wilson-Cook Endoscopic Suturing Device, NDO Plicator, Enteryx, Gatekeeper Reflux Repair System and Plexiglas. Three procedures were compared with control cases (Stretta procedure, Bard EndoCinch and Enteryx). The results of patients in the treatment group were good or significantly better than those of the control group in terms of reflux, burning, quality of life and consumption of proton pump inhibitors. Two endoscopic procedures were compared with laparoscopic fundoplication, Stretta procedure and Bard EndoCinch device. Endoscopic patient outcomes were in conflict. Some patients in the endoscopic group found comparable results compared to patients undergoing laparoscopic approach, while others experienced lower results. The authors concluded that there is not enough evidence to determine the safety and efficacy of endoscopic procedures for gastro-oesophageal reflux disease, especially in the long term.

Medical management: Medical management of gastroesophageal reflux disease is the most commonly used one [46]. It begins with dietary and life-giving advice, up to pharmacological management, which can be "step up" or "step down". Step up approach provides the advantage of minimum usage of drugs and PPIs (Proton Pump Inhibitors). Step down approach provides faster symptom relief.

The step-up therapy for GERD is preferable in patients with mild and intermittent symptoms (fewer than two episodes per week) who have no evidence of erosive esophagitis on upper endoscopy. It consists of the following timing:

- **First step:** lifestyle and dietary modification +/- low-dose H2RAs (histamine H2-receptor antagonists) +/- antacids. H2 RAS (H2 antagonists or H2-histamine receptor antagonists), also called H2 blockers, are a class of drugs that block the action of histamine on H2 receptors of histamine of the parietal cells in the stomach. This decreases the production of stomach acid [47]. The histamine H2

receptors are antagonist molecules of histaminergic receptors, which - being no longer activated - inactivate the proton pump and reduce the release of hydrogen ions; these drugs act mainly on nocturnal acid secretion, but also on the secretion induced by the ingestion of food. They are administered orally, although in that case undergo a first pass liver effect that reduces the bioavailability of 50%, or by parenteral route in case of emergency. This pharmacology category can also be used for the treatment of gastro-oesophageal reflux, for digestive difficulties and acute stress ulcers. This class of antisecretory is now very little used. The antacids are symptomatic medications with fast action, useful for casual use, but not suitable for chronic therapies. The most common antacids are baking soda, aluminum and magnesium hydroxides, capable of temporarily neutralize the hydrochloric acid secretion by the parietal cells. The aluminum and magnesium hydroxides are used concomitantly (Maalox) to balance the respective side effects; in the case of the aluminum hydroxide is constipation, in the case of magnesium hydroxide is diarrhea. The administration of bicarbonate helps the rapid elimination of acidic substances by the kidney, but in excessive doses can cause hypernatremia and alkalosis generalized. Antacids are OTC drugs (over the counter) used for treatment of occasional burning pain in the stomach and digestive difficulties.

- **Second step:** lifestyle and dietary modification +/- standard dose H2RAs +/- antacids
- **Third step:** lifestyle and dietary modification +/- low-dose PPIs (once daily) +/- antacids.

The proton pump inhibitors (PPIs inappropriately also known as Prazoli) are a group of molecules whose main action is a pronounced reduction of long duration (from 18 to 24 h) acidity of gastric juices [48]. The group of PPIs is the successor of H₂ antihistamines (such as ranitidine) and are largely the most common of the latter for their increased effectiveness. This type of medicinal inhibits the gastric enzyme H⁺/K⁺ -ATPase (the proton pump), the catalyst of the exchange of H⁺ ions and K⁺. This effectively creates an inhibition on acid secretion. In the micro-channel, where the pH is low, close to 2, these inhibitors are ionized and turned into molecules that establish covalent bonds with the thiol group (SH) of cysteine of the sub-units of the pump. So doing, the pump is inhibited irreversibly.

The resumption of pumping requires the production of new pumps. On average, the time for the synthesis of new pumps is between 18 and 24 h. A single dose allows an inhibition of about 24 h. The fact that the inhibitors are active only in acidic environment, before protonation, explains that they have a minimal effect on H⁺/K⁺ -ATPase extra-gastric, situated at the level of the rectum and colon. The Cl⁻ secretion, that is parallel to that of H⁺ to produce HCl, is not directly modified by inhibitors of H⁺/K⁺ -ATPase. The Cl⁻ secretion mechanism remains poorly understood. It seems, however, be linked to that of potassium, which allows the recycling of the latter. A consequence of the H⁺/K⁺ -ATPase is the exponential increase gastric gastrin, very important in mice, but of little relief in humans. The hypergastrinaemia could give way to a hyperplasia of the enterochromaffin cells. Proton pump inhibitors (PPIs) are widely used in the treatment of acid regurgitation related gastric disorders such as gastroesophageal reflux disease, peptic ulcer and Zollinger-Ellison syndrome. PPI treatment of gastrointestinal disorders related to acid regurgitation generally requires long-term administration, which increases the possibility of clinically significant drug interactions. This problem is particularly relevant in patients undergoing polypharmotherapy, such as hospitalized and elderly people. In a

previous review published in 2006, the analogy and differences between the various PPIs were studied in terms of potentiality, importance and mechanism of pharmacological interactions. The results of this review highlighted high potential for drug interaction for omeprazole due essentially to high affinity for cytochrome 2C-19 and moderate affinity for cytochrome 3-A4. Conversely, pantoprazole exhibited low potency of drug interaction. Interaction with clopidogrel, rather than a class effect, seems to be an effect bound to the single molecule. Indeed, although recent retrospective studies have suggested a decrease in the efficacy of clopidogrel when administered simultaneously to a PPI, the stratification of the assay showed that such effects are detectable in patients with omeprazole therapy, but not among those treated with sodium pantoprazole.

The explanation lies in the fact that clopidogrel is converted into its active metabolite by cytochrome 2C-19, an enzyme that can be inhibited by omeprazole but not by pantoprazole. Lansoprazole and dexpanoprazole also did not show significant interaction with clopidogrel, unlike esomeprazole which exhibited similar behavior to omeprazole. Both in the 2006 review and in this latest, pantoprazole sodium showed a potential for very low drug interaction compared to other drugs of its class: it does not interfere with clopidogrel and does not result in any significant metabolic interaction when used in combination with antacids, NSAIDs, Cardiovascular drugs, SNC drugs, immunosuppressants, endocrine and metabolism drugs, and others. The results of this study clearly show how individual PPIs exhibit different potentials of pharmacological interaction. The studies conducted so far indicate for omeprazole a remarkable potential for interaction due to the greater affinity of this molecule for cytochromes 2C-19 and 3A4. Conversely, pantoprazole has a very low drug interaction potential. In particular, omeprazole and esomeprazole appear to interact with clopidogrel by reducing their bioavailability, while lansoprazole, rabeprazole and, above all, sodium pantoprazole due to their low affinity for specific CYP isoenzymes or for the involvement of additional elimination processes present significantly lower pharmacological interaction rates. Potential differences in pharmacological interaction are very important determinants in the choice of a PPI for the management of gastrointestinal disorders related to acid regurgitation. This aspect is particularly relevant in elderly patients, almost constantly undergoing polypharmotherapy, or in patients taking drugs with a narrow therapeutic window. Pantoprazole, with its low risk profile of drug interactions, widely documented in the literature, could represent the drug of choice in such categories of patients [49].

- **Fourth step:** lifestyle and dietary modification +/- standard dose PPIs +/- antacids

The step-down therapy is appropriate for Patients with erosive esophagitis, for Patients with frequent symptoms (two or more episodes per week) and for Patients with severe symptoms that impair quality of life. It consists of the following timing:

- **First step:** lifestyle and dietary modification+standard-dose PPI once daily
- **Second step:** lifestyle and dietary modification+low-dose PPIs
- **Third step:** lifestyle and dietary modification+H2RAs
- **Fourth step:** lifestyle and dietary modification+acid suppression discontinued

In case of severe esophagitis and/or Barrett's esophagus, maintenance PPI therapy is preferable. Rare and minimal side effects of PPIs are: iposideremia, anemia, hypocalcemia, osteoporosis,

cardiovascular problems, malabsorption of trace elements, easy to infection. Lifestyle modifications consist in weight loss, elevation of head end of the bed in patients with nocturnal or laryngeal symptoms, refraining from assuming a supine position after meals and avoidance of meals two to the hour before bedtime. Dietary modification consist in elimination of dietary triggers, avoid sweets, especially mint, and chewing gum, avoidance of tobacco and alcohol, abdominal breathing exercise. In selected cases, physical therapy can be helpful, especially the global postural physiotherapy. Antacids are a combination of magnesium trisilicate, aluminum hydroxide or calcium carbonate.

They neutralize gastric pH and give relief of heartburn within five mins, but with short duration of effect of 30 to 60 mins. H2 receptor antagonists decrease the secretion of acid by inhibiting the histamine 2 receptor on the gastric parietal cell. They have slower onset of action, around 2.5 h and significantly longer duration of action than antacids of 4 to 10 h. But they give tachyphylaxis within 2-6 weeks of initiation. Proton pump inhibitors irreversibly bind and inhibit the H-K ATPase pump. They should be administered daily rather than on-demand. Standard doses for eight weeks relieve symptoms of GERD and heal esophagitis in up to 86% of patients with erosive esophagitis. Proton pump inhibitors have potential adverse events. A study summarizes the potential adverse effects of proton pump inhibitors (PPI), including nutritional deficiencies (B12 and magnesium), acid rebound hypersecretion, acute interstitial nephritis, gastric cancer, cardiovascular risk (in case of administration concomitant with Clopidogrel), bone fractures and pneumonia.

An epidemiological statistical equation is considered to assess the clinical relevance of these events and to reinforce recommendations on the best solutions. Evidence of adverse events associated with proton pump inhibitors is limited by the absence of level 1 studies (controlled randomized trials). The best evidence supports *Clostridium difficile* infection and bone fractures in risk populations treated with these drugs. Significant reduction in gastrointestinal bleeding without increased cardiovascular events was observed in the COGENT study when clopidogrel was administered with pantoprazole. The risk of pneumonia is inconsistent, and although acute interstitial nephritis, nutritional deficiencies (including B12 and hypomagnesaemia), gastric carcinoid and rebound hyperacidity are biologically plausible, studies have failed to demonstrate clinical relevance. The synthesis of this study was the recommendation to prescribe PPIs only for proven evidence. There is no reliable data supporting the risk of adverse events. However, the advice is to exercise caution in the elderly and in patients with other risk factors for bone fractures or *C. difficile* infection [50].

Problem of GERD recurrent symptoms

Total 2/3rd of patients with non-erosive reflux disease and all patients with erosive esophagitis relapse when acid suppression is discontinued. If recurrence happens after 3 months of discontinuation, it is necessary repeat 8 weeks course of acid suppressive therapy. If recurrence happens before 3 months of discontinuation, upper GI endoscopy must be repeated to rule out complications and long term acid suppressive therapy. We define refractory GERD a partial or lack of response to PPI twice daily.

Conclusions

Endoscopic full-thickness plication using multiple Plicator implants can be used safely and effectively to improve GERD symptoms and

reduce medication use in selected Patients. The safety and efficacy of endoscopic therapies for the treatment of GERD have not been established in the published medical literature. Current studies are generally of small to moderate size, lack adequate control or comparison groups, and provide only short-term follow-up. Further well-designed clinical trials with long-term follow up are required to establish that endoscopic therapies benefit health outcomes in patients with GERD by eliminating symptoms, preventing recurrence of symptoms or progression of disease, healing esophagitis, and reducing the need for pharmacologic therapy [9].

Despite the effort of resolving gastroesophageal reflux with mini-invasive or, even better, endoscopic surgical procedures, the experience of real life teaches us that the patients are oriented to medical treatment and the use of surgical procedures is reserved for reduced cases. In particular, the use of surgery occurs in the case of non-responders, in the case of gastro-laryngeal reflux and in the case of young people who have difficulty in maintaining constant attention to the taking of medicines. Gastroesophageal reflux disease is a very common disease among the "healthy". Medical treatment is the simplest and most preferred one. Proton pump inhibitors are the most performing drugs and alarms on their side effects do not have sufficient evidence in the literature. Treatment of gastroesophageal reflux is recommended to improve the quality of life and, above all, to avoid serious complications. The address to laparoscopic or endoscopic surgery is reserved for special and well-studied cases.

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