Laparoscopic Nissen Fundoplication in the Treatment of Gastroesophageal Reflux Disease

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Abstract

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of gastric contents into the esophagus leads to troublesome symptoms and/or complications. Heartburn is the cardinal symptom, often associated with regurgitation. In patients with endoscopy-negative heartburn refractory to proton pump inhibitor (PPI) therapy and when the diagnosis of GERD is in question, direct reflux testing by impedance-pH monitoring is warranted. Laparoscopic fundoplication is the standard surgical treatment for GERD. It is highly effective in curing GERD with a 80% success rate at 20-year follow-up. The Nissen fundoplication, consisting of a total (360°) wrap, is the most commonly performed antireflux operation. To reduce postoperative dysphagia and gas bloating, partial fundoplications are also used, including the posterior (Toupet) fundoplication, and the anterior (Dor) fundoplication. Currently, there is consensus to advise laparoscopic fundoplication in PPI-responsive GERD only for those patients who develop untoward side-effects or complications from PPI therapy. PPI resistance is the real challenge in GERD.
Keywords: Laparoscopic Nissen Fundoplication, Gastroesophageal Reflux Disease

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Introduction

Gastroesophageal reflux disease (GERD) is currently defined as a condition that develops when the reflux of gastric contents into the esophagus leads to troublesome symptoms and/or complications[1-4]. GERD is the most common disease encountered by the gastroenterologist with a 20% prevalence in the adult population. It has been classified as the presence of reflux symptoms without erosions on endoscopic examination, *i.e.*, nonerosive reflux disease (NERD) or reflux symptoms with mucosal breaks at endoscopic examination, *i.e.*, erosive reflux disease (ERD)[3].

ERD is found in up to 20% of GERD patients and should be regarded as the most common complication of GERD rather than its principal manifestation[4]. Esophageal peptic ulcers and strictures have become quite uncommon in the proton pump inhibitor (PPI) era[4].

Barrett's esophagus is a condition in which the stratified squamous esophageal epithelium is replaced by endoscopically detectable columnar metaplasia[5,6] : it occurs in 2% of the general adult population and represents the most dreaded complication of GERD because it predisposes to esophageal adenocarcinoma, the fastest growing cause of cancer mortality. There is still debate about the working definition of Barrett's esophagus[5,6]. According to the American Gastroenterological Association, Barrett's esophagus is a change in the distal esophageal epithelium of any length that can be recognized as columnar type mucosa at endoscopy and is confirmed to have intestinal metaplasia by biopsy of the tubular esophagus[5]. According to the British Society of Gastroenterology, only 1 cm or more of endoscopically visible columnar epithelium above the gastroesophageal junction dictates biopsy sampling, whereas the detection of intestinal metaplasia is not a prerequisite for the definition of Barrett's esophagus but only for the necessity of endoscopic surveillance[6].

The typical reflux syndrome includes heartburn and regurgitation. Heartburn is the cardinal GERD symptom and is defined as a burning sensation in the retrosternal area, behind the breastbone. Regurgitation is defined as the perception of refluxed gastric content into the mouth or hypopharynx.

Atypical reflux syndromes include noncardiac chest pain (NCCP) and extraesophageal syndromes. NCCP consists of chest pain indistinguishable from ischemic cardiac pain in patients in whom cardiac disease has been carefully excluded: it can be caused by GERD, mainly when it is associated with heartburn, or by esophageal motility disorders. Extraesophageal syndromes include chronic cough, chronic asthma, chronic laryngitis, and dental erosions: a cause-and-effect relationship between extraesophageal syndromes and reflux can be shown in few patients only, more often in those also complaining of heartburn.

Associated syndromes include dyspepsia (epigastric pain/burn, post-prandial fullness, early satiety) and irritable bowel syndrome (abdominal pain or discomfort with disturbed bowel habit and/or bloating): no causal link with reflux has been shown but these syndromes can be found in up to 50% of patients with GERD.

DIAGNOSIS

ERD and Barrett's esophagus are found at endoscopy in up to 30% of patients with the typical reflux syndrome. Accordingly, endoscopic assessment is recommended only in the presence of alarm symptoms (dysphagia, vomiting, anemia, involuntary weight loss) and the diagnosis of GERD is currently patient-centered, based on the presence of heartburn with/without regurgitation and on a positive response to a PPI therapeutic trial[1,3], given the extraordinary high efficacy of PPIs in providing rapid heartburn relief and mucosal healing in ERD. The current definition of NERD, *i.e.*, reflux symptoms without erosions at endoscopic examination[3,4] does not completely fit with the

definition of disease, however. A disease is a morbid entity characterized by at least two of three criteria: (1) recognized etiologic agent(s); (2) identifiable group of signs and symptoms; and (3) consistent anatomic alterations[4]. In patients with endoscopy-negative heartburn, *i.e.*, without consistent anatomic alterations, to make a diagnosis of disease (NERD) we must rely upon the efficacy of PPIs in suppressing acid reflux-related symptoms, acid reflux being then identified as the etiologic agent of the typical reflux syndrome. However, between 10% and 30% of patients with heartburn remain symptomatic on standard and even high PPI dosages[7]. In these cases, direct reflux monitoring is warranted to distinguish patients with reflux-related PPI-unresponsive heartburn, *i.e.*, refractory NERD from those with reflux-unrelated endoscopy-negative PPI-unresponsive heartburn, *i.e.*, functional heartburn (FH)[8]. Direct reflux monitoring is also indicated in all other situations when the diagnosis of GERD is in question, *i.e.*, NCCP and extraesophageal syndromes in patients not complaining of heartburn.

Traditional and wireless pH-monitoring have limited accuracy in studying reflux because they only detect reflux episodes with a pH < 4.0. Gastroesophageal refluxate contains a variety of noxious agents, including hydrochloric acid and pepsins. PPI therapy transforms the vast majority of acid refluxes into weakly acidic refluxes[9]. As the proteolytic activity of pepsins is essential for mucosal damage to occur and is maintained up to pH 6, weakly acidic refluxes can damage esophageal mucosa and have been implicated in the pathogenesis of ERD persisting despite PPI therapy[10].

Impedance-pH monitoring provides a complete assessment of reflux, allowing detection of acid, weakly acidic, and weakly alkaline refluxes, and should be regarded as the gold standard for distinguishing patients with reflux-related from those with reflux-unrelated syndromes[8,11]. In patients evaluated off PPI therapy, impedance-pH monitoring criteria afford a 12% diagnostic gain over pH-only criteria, allowing identification of NERD patients even when esophageal acid exposure is normal by means of a positive symptom-reflux association with nonacid refluxes[12]. However, off-PPI impedance-pH criteria to distinguish NERD from FH have not yet been validated by outcome studies in the clinical setting of PPI refractoriness. By adding quantitative analysis of impedance-pH parameters to symptom-reflux association, a subdivision of PPI-refractory patients into refractory NERD and FH can be obtained by on-PPI impedance-pH monitoring[13] which is substantiated by pathophysiological findings peculiar to GERD[14] as well as by outcome data[15-18]. In this respect, a recently developed new quantitative parameter, namely the post-reflux swallow-induced peristaltic wave index, allows a clear-cut separation of NERD from FH in patients evaluated off- as well as on-PPI therapy[19]. By adding quantitative analysis of on-PPI impedance-pH parameters to symptom-reflux association, NERD was diagnosed in two thirds of endoscopy-negative PPI-refractory patients as opposed to less than half of cases using symptom-reflux association only[13]. Therefore, on-PPI impedance-pH monitoring represents a cost-effective diagnostic strategy in patients with PPI-unresponsive typical reflux syndrome, validated by outcome studies[15-18]. On the other hand, given the low probability that NCCP and respiratory symptoms are due to reflux in the absence of heartburn,

patients with atypical symptoms only should be assessed with impedance-pH monitoring after PPI withdrawal[3,11].

MEDICAL MANAGEMENT

PPIs represent the mainstay of medical treatment in GERD[1,3]. They provide the most rapid symptomatic relief and heal esophagitis in the highest percentage of patients[1,3], transforming the vast majority of acid refluxes into weakly acidic refluxes[9]. However, typical GERD symptoms recur within 1 year in more than 90% of patients after PPI-withdrawal, in many of them within few days. Moreover, up to 30% of patients with heartburn[7] and even more patients with regurgitation[20] fail to respond, either partially or completely, to PPI therapy at standard and even high dosages. Laparoscopic fundoplication is the only treatment modality currently recommended for overcoming PPI failures[1-3].

SURGICAL MANAGEMENT

Fundoplication is the standard surgical treatment for GERD. The question of laparoscopic *vs* open surgery is no longer relevant. Randomized studies and meta-analyses have shown that laparoscopic fundoplication should be preferred over the open alternative: efficacy is comparable but mortality is lower (0.04% *vs* 0.2%) and cosmesis is undoubtedly better[21].

Many studies have shown that laparoscopic fundoplication is highly effective in curing PPI-responsive GERD, long-term postoperative assessment consisting of symptom evaluation[21-26]: persistent relief of heartburn and regurgitation has been reported in 90% and 80% of patients at 10-year[22-24] and 20-year follow-up[21,25,26], respectively, with less than one half of those few patients with recurrent heartburn having evidence of abnormal reflux[22].

The Nissen fundoplication, consisting of a total (360°) wrap, is the most commonly performed antireflux operation. Dysphagia and gas bloating are the primary causes of dissatisfaction despite general reflux alleviation[27]. Aiming to reduce postoperative dysphagia and gas bloating, a variety of procedures in which the fundus is only partially wrapped have been proposed, including the Toupet fundoplication, consisting of a posterior (270°) wrap, and the Dor fundoplication, consisting of an anterior (180°) wrap. Recent studies suggest that anterior fundoplication is as effective as total fundoplication in terms of reflux and heartburn/regurgitation control with less dysphagia and gas bloat[28-30]. Likewise, at 6-12 mo after intervention, similar efficacy on heartburn/regurgitation and reflux parameters have been reported when Toupet and Nissen fundoplications have been compared but with less dysphagia and gas bloat with the former (3% and 23%) than with the latter (7% and 36%)[31-33]: however, it should be noted that such differences are minor and that with both the techniques the fundoplication was performed by fixing the wrap to the anterior wall of the esophagus. The Nissen procedure can also be carried out without anchoring the fundoplication: no wrap slipping, negligible gas bloating, and cumulative incidence of postoperative dysphagia quite similar to that of the Toupet procedure, in conjunction with normal reflux parameters and sustained symptom

remission in the vast majority of cases have been reported[15-18]. To prevent postoperative dysphagia, other key technical issues must be considered including division of the short gastric vessels whenever deemed necessary in order to adequately mobilize the esophagus and to make the fundoplication tension-free, and insertion of a 52-Fr bougie into the esophagus during construction of the wrap[2,15-18]. Finally, the reported differences in postoperative side-effects favoring the partial wrap disappear after 2 decades of follow-up[25].

Table 1 Indications for laparoscopic fundoplication

AGA	Patients with esophagitis who are intolerant of PPI therapy
	Patients with symptoms of the esophageal GERD syndrome poorly controlled by PPI therapy, especially in the setting of persistent troublesome regurgitation
	Carefully selected patients with extraesophageal GERD syndromes in whom a reflux causality has been established to the greatest degree possible
SAGES	Patients who have failed medical management (inadequate symptom control, severe regurgitation not controlled with acid suppression, or medication side-effects)
	Patients who opt for surgery despite successful medical management
	Patients who have complications of GERD (*e.g.*, Barrett's esophagus, peptic stricture)
	Patients who have extra-esophageal manifestations (asthma, hoarseness, cough, chest pain, aspiration)
ACG	Surgical therapy is a treatment option for long-term therapy in GERD patients
	Surgical therapy is generally not recommended in patients who do not respond to PPI therapy
	Refractory patients with objective evidence of ongoing reflux as the cause of symptoms should be considered for additional antireflux therapies, which may include surgery
	Surgery should generally not be performed to treat extraesophageal symptoms of GERD in patients who do not respond to acid suppression with a PPI

PPI: Proton pump inhibitor; GERD: Gastroesophageal reflux disease; AGA: American Gastroenterological Association; SAGES: Society of Gastrointestinal and Endoscopic Surgeons; ACG: American College of Gastroenterology.

PPI-responsive typical GERD

According to the American Gastroenterological Association, GERD patients who are well maintained on medical therapy have nothing to gain from laparoscopic fundoplication and should be advised against surgery[1]. On the other hand, guidelines from the American College of Gastroenterology state that surgical therapy is a treatment option for long-term therapy in GERD patients[3]. A recent multicenter trial showed that most PPI-responsive GERD patients achieve and remain in heartburn remission at 5 years with laparoscopic fundoplication or esomeprazole in a dose-escalating manner when required, with a higher prevalence of dysphagia and gas-bloating and a lower prevalence of regurgitation in the surgically-treated patients[34]. In advising laparoscopic fundoplication to PPI-responsive GERD patients, side effects and complications of laparoscopic fundoplication[35] and the excellent safety profile of PPIs[36] should be taken into account. Fundic gland polyps are a frequent complication of prolonged PPI therapy but are considered potentially harmful only when larger than 1 cm[37]. Therefore, in PPI-responsive patients the current consensus is to advise antireflux surgery only for those few patients who develop untoward side-effects or complications from PPI therapy (Table 2).

Table 2 Side-effects and complications of proton pump inhibitors

Headache (< 2%)
Diarrhea (< 2%)
Malabsorption of magnesium, calcium, vitamin B12, iron (doubtful)
Increased risk of *Clostridium difficile* colitis in antibiotic users (doubtful)
Increased risk of pneumonia (doubtful)
Acute interstitial nephritis (extremely rare)
Drug-drug interactions (doubtful)
Accelerated progression of *Helicobacter pylori* gastritis (doubtful)
Formation of gastric fundic gland polyps (potentially harmful when > 1 cm)

As far as endoscopic treatment modalities are concerned, the usage of current endoscopic therapies cannot be recommended as an alternative to medical or traditional surgical therapy[3]. A laparoscopically implanted sphincter augmentation device has recently been proposed[38] but more data on long-term efficacy, safety, and costs are required before widespread usage can be recommended[3].

Before surgical intervention impedance-pH monitoring is warranted, always preceded by esophageal manometry to rule out severe esophageal motility disorders[1-3]. Impedance-pH monitoring should be performed during PPI withdrawal and only after symptoms have recurred in order to assess symptom-reflux association and identify patients with esophageal hypersensitivity (positive symptom-reflux association with normal reflux parameters) because they can benefit from laparoscopic fundoplication[39]. In patients with negative impedance-pH results FH is the most likely diagnosis, PPIs resumption should be postponed, and only watchful follow-up is warranted.

CONCLUSION

Laparoscopic fundoplication is highly effective in curing GERD. However, considering its side effects laparoscopic fundoplication should be advised only for those few PPI-responsive GERD patients who develop side-effects or complications from PPI therapy. Currently, the main indication for laparoscopic fundoplication is represented by PPI-refractory GERD, provided that objective evidence of reflux as the cause of ongoing symptoms has been obtained by impedance-pH monitoring.

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