



ORIGINAL ARTICLE

A comparison of medical versus surgical treatment in Barrett's oesophagus acid control[☆]



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Abstract

Introduction: Barrett's oesophagus (BE) is an oesophageal injury caused by gastroesophageal acid reflux. One of the main aims of treatment in BE is to achieve adequate acid reflux control. **Objective:** To assess acid reflux control in patients with BE based on the therapy employed: medical or surgical.

Methods: A retrospective study was performed in patients with an endoscopic and histological diagnosis of BE. Medical therapy with proton pump inhibitors (PPI) was compared with surgical treatment (Nissen fundoplication). Epidemiological data and the results of pH monitoring (pH time <4, prolonged reflux >5 min, DeMeester score) were evaluated in each group. Treatment failure was defined as a pH lower than 4 for more than 5% of the recording time.

Results: A total of 128 patients with BE were included (75 PPI-treated and 53 surgically-treated patients). Patients included in the two comparison groups were homogeneous in terms of demographic characteristics. DeMeester scores, fraction of time pH <4 and the number of prolonged refluxes were significantly lower in patients with fundoplication versus those receiving PPIs ($p < .001$). Treatment failure occurred in 29% of patients and was significantly higher in those receiving medical therapy (40% vs 13%; $p < .001$).

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PALABRAS CLAVE

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Conclusions: Treatment results were significantly worse with medical treatment than with anti-reflux surgery and should be optimised to improve acid reflux control in BE. Additional evidence is needed to fully elucidate the utility of PPI in this disease.

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Estudio comparativo del tratamiento médico frente al quirúrgico en el control ácido del esófago de Barrett

Resumen

Introducción: El esófago de Barrett (EB) es una lesión esofágica ocasionada mayoritariamente por reflujo gastroesofágico ácido. El control del reflujo ácido es uno de los principales objetivos del tratamiento de esta patología.

Objetivo: Evaluar en nuestra área de salud el grado de control del reflujo ácido en los pacientes con EB en función del tratamiento de mantenimiento recibido, médico o quirúrgico.

Métodos: Estudio retrospectivo de pacientes con diagnóstico endoscópico e histológico de EB. Un grupo de pacientes recibió tratamiento médico con inhibidores de la bomba de protones (IBP) y otro grupo fue sometido a intervención quirúrgica (funduplicatura de Nissen). Se compararon datos epidemiológicos y resultados de pHmetría (tiempo de pH < 4, reflujo prolongado > 5 min, puntuación de DeMeester) de cada grupo. La pH-metría se realizó con IBP en el grupo de tratamiento médico y en el grupo de cirugía sin consumo de antisecretorios ácidos. Se definió fracaso del tratamiento como un pH < 4 total superior al 5%.

Resultados: Fueron incluidos 128 pacientes con EB (tratamiento médico 75, tratamiento quirúrgico 53). Ambas cohortes eran homogéneas respecto a sus características demográficas. Las puntuaciones de DeMeester, fracción de tiempo de pH < 4 y cantidad de reflujo prolongado fueron significativamente inferiores en los pacientes con funduplicatura frente a los que recibían IBP ($p < 0,001$). De forma global se apreció un fracaso de tratamiento en el 29% de los pacientes, que fue significativamente mayor en el grupo de tratamiento médico (40% vs 13%; $p < 0,001$).

Conclusiones: El grado de control del reflujo ácido gastroesofágico es subóptimo en un elevado porcentaje de pacientes con EB. El tratamiento médico ofrece resultados inferiores a la cirugía antirreflujo y se debería intentar optimizar sus resultados.

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Introduction

Barrett's oesophagus (BO) is characterised by replacement of the oesophageal squamous epithelium by metaplastic columnar epithelium. BO, an oesophageal injury caused by severe, chronic gastro-oesophageal reflux,¹ is the primary risk factor for developing oesophageal adenocarcinoma (OAC), with a 30- to 50-fold increased risk compared to the general population.² Nevertheless, only a small proportion of patients with BO develop OAC; annual incidence is estimated at 0.27%, or 0.61% for a combined risk of high-grade dysplasia and OAC.^{3,4} For this reason, screening and surveillance programmes for high-risk patients have been implemented in developed countries.⁵ Some studies have reported a considerable increase in the incidence of OAC over the past 30 years in countries such as the USA.⁶ This is evidence of both shortcomings in existing screening programmes and the existence of other external factors, apart from BO, involved in the carcinogenic process. Studies have shown obesity and an unhealthy diet to be independent risk factors for OAC, even in the absence of gastro-oesophageal reflux disease (GORD).⁷

Strategies for treating gastro-oesophageal reflux include medical therapy, to inhibit gastric acid secretion, and surgery. Both have been shown to initially improve symptoms, reduce the acid reflux that damages the oesophageal mucosa, and halt the carcinogenic process.^{4,8,9} Among the drugs available to treat BO, proton pump inhibitors (PPI) have been shown to be the most effective in reducing gastric acid production, controlling GORD symptoms, and increasing mucosal healing in patients with oesophagitis. Acid suppressants are not usually entirely successful in controlling either symptoms or acid secretion, above all in long-segment BO (>3 cm), which is more refractory to conventional dosing regimens.¹⁰ Evidence suggests that control of symptoms is not always associated with control of acid reflux measured by pH monitoring.¹¹ Some clinical trials have reported a lower incidence of dysplasia and cancer in patients with BO undergoing Nissen fundoplication compared with those receiving medical treatment, although these preliminary findings were not confirmed in later, more methodologically sound studies.^{12,13}

BO is the primary risk factor for OAC, and clinical symptoms do not reflect pH acidity levels, therefore, controlling

symptoms such as pyrosis, burning sensation or chest pain is insufficient; acid reflux inhibition should be the primary therapeutic objective in patients with BO.¹⁴

The aim of this study was to evaluate acid reflux control in patients with BO in our healthcare catchment area, according to whether they received medical or surgical treatment.

Methods

We conducted a single-centre, retrospective, descriptive, comparative study in the gastroenterology department of the Leon University Hospital. The records of all patients diagnosed with BO between January 2003 and December 2013 on the basis of endoscopic and histological findings who underwent 24-h ambulatory oesophageal pH monitoring were included in the study.

Patients were selected from the pH monitoring records maintained in our Gastrointestinal Motility Unit. All patients previously diagnosed with BO who had undergone oesophageal pH monitoring to evaluate response to acid reflux management strategies were included.

The pH monitoring was performed by a single specialist and nurse from our Motility Unit. All tests were performed during the morning, following a 10-h fast. On the day of the test, patients were instructed to pursue their normal everyday activities, avoiding physical exertion, and to record on a chart the time spent upright or supine, as well as each episode of reflux, belching or vomiting occurring during the day.

Study patients (n=128) were divided into 2 groups, according to treatment:

1. Medical treatment with PPIs (n=75). PPIs were taken in a single- or double-dose regimen, as prescribed by the patient's physician. In all cases, monitoring was performed at least 1 year after starting PPI treatment. The medication was not suspended during the study, as the objective was to evaluate the extent to which the treatment controlled acid reflux. Standard treatment was defined as a single-dose PPI regimen, and double-dose was defined as 2 doses of PPI per day. The pH monitoring was not only performed due to persistence of symptoms, but also to evaluate response to treatment and/or as a part of the preoperative workup.
2. Surgical treatment: laparoscopic Nissen fundoplication (n=53). This group included patients undergoing pH monitoring 1 year after surgery to evaluate response to treatment. Patients undergoing pH monitoring due to clinical worsening or when monitoring was ordered for reasons other than follow-up less than 1 year after surgery were excluded. None of the surgical patients underwent pH monitoring while also on PPI therapy. In most cases, surgery had been indicated following persistence of symptoms due to lack of response to medical treatment. Surgery was performed to prevent progress of long-segment BO in 19 young patients.

Length of BO as recorded on the endoscopy database was defined as short-segment (less than 3 cm) or long-segment (greater than 3 cm).

The following 24-h oesophageal pH monitoring parameters were recorded:

- Fraction of total time with pH <4, in the supine position and upright, expressed as a percentage.
- DeMeester score.
- Number of reflux episodes lasting >5 min in total, in the upright position and supine.

Reports from all pH monitoring tests were obtained for all BO patients. The patient's motility history was examined to obtain epidemiological information and details of the treatment administered (PPI, dosage) at the time of the test, and the reason the test was requested. Details of the histological diagnosis and length of the BO were extracted from the endoscopy records kept in our department and on the hospital's intranet service. Once all the data had been gathered, epidemiological variables, fraction of total time with pH <4 in both upright and supine position, number of reflux episodes lasting >5 min in total in both upright and supine position, and DeMeester score were compared between patients receiving medical treatment with PPIs and surgery (Nissen fundoplication).

Uncontrolled acid reflux, indicating therapeutic failure, was defined as DeMeester score > 15 or fraction of total time with pH <4 greater than 5% on the pH monitoring.

Statistical analysis was performed using PASW statistics 18 (SPSS). Qualitative variables are expressed as absolute number and percentage. Quantitative variables are expressed as mean and standard deviation. The Chi-square test was used to compare quantitative variables, and the Student's *t* or Mann-Whitney *U* tests were used to evaluate differences between means of quantitative variables. Differences in quantitative variables between patients were compared using the Wilcoxon test. The Spearman correlation coefficient was used to measure the strength of association between 2 quantitative variables.

Results

A total of 128 patients (97 men and 31 women) were included, with a mean age of 49 years. Most (87 patients, 68%) presented short-segment BO. Half of all medical patients followed a standard PPI regimen, and half a double-dose regimen (PPI/12 h). The most commonly used PPI (21% of all cases) was lansoprazole.

Table 1 compares outcomes in medical and surgical patients. Men outnumbered women in the surgical group and also in the long-segment BO group; 36% of long-segment cases underwent surgery compared with 30% receiving medical treatment. As can be seen, percentage of time with pH <4 and DeMeester scores were significantly lower among patients undergoing surgical treatment. The groups were evenly matched in terms of body weight and time from diagnosis, although age differences were observed between groups, as shown in Table 1.

Length of BO was compared between groups (Table 2). Of a total of 41 patients with long-segment BO, 46.3% (n=19) underwent surgery compared with only 39% of the 87 patients (n=34) with short-segment BO. The total number or episodes of reflux lasting <5 min, fraction of total

Table 1 Patient characteristics by type of treatment received.

	Anti-reflux surgery (n = 53)	Medical treatment (n = 75)	p
Men	43 (81%)	54 (72%)	0.235
Long-segment Barrett's	19 (36%)	22 (30%)	0.34
Age	48.40 ± 9.41	50.72 ± 12.71	0.025
Weight	76.04 ± 11	72.97 ± 12.28	0.679
Total number of refluxes >5 min	5.06 ± 6.6	6.49 ± 6.6	0.248
Fraction of time with pH <4(%)	5.563 ± 13.07	19.666 ± 82.56	<0.001
Upright	5.184 ± 11.75	15.771 ± 48.60	<0.001
Supine	10.60 ± 21.53	17.557 ± 40.26	0.025
DeMeester	18.147 ± 31.07	57.78 ± 73.2	<0.001

Data shown as mean ± standard deviation.

time with pH <4, fraction of time upright with pH <4, and DeMeester score were all significantly lower in patients with short-segment BO ($p < 0.05$).

Overall, 37/128 cases (29%) presented uncontrolled acid reflux. In this regard, a substantial difference was observed between groups: therapeutic failure was observed in up to 40% of patients receiving medical treatment vs only 13% of surgical cases ($p < 0.001$).

In the surgical group (n = 53 patients), pH monitoring was performed both before and after the procedure in 19 cases. The 19 patients undergoing pre-surgical pH monitoring were receiving medical treatment, whereas in these same patients, as in the rest of the surgical group, post-surgical monitoring was performed without medication. An analysis of this group showed a significant reduction in all parameters following surgery ($p < 0.01$). Prior to surgery, moreover, acid reflux was controlled in only 37% of these patients, while in the post-surgery studies up to 95% presented good control.

Discussion

Ambulatory oesophageal pH monitoring is the only study that directly measures oesophageal acid exposure. It is indicated in patients with persistent GORD symptoms despite PPI therapy, above all in cases where endoscopy is negative for GORD. It is used to evaluate response to treatment in patients receiving therapy and to confirm diagnosis in patients scheduled for surgery.¹⁵ Impedance-pH monitoring, which also measures non-acid reflux, is currently used to obtain a more accurate diagnosis. Indications for surgery are

well established: intolerance of medical therapy, lifelong medical treatment ruled out, presence of GORD refractory to optimal medical treatment, reflux associated with large hiatal hernia or morbid obesity with indication for surgery.

Using our patient records, we retrospectively evaluated response to these 2 standard strategies for treating GORD in patients with a histopathological diagnosis of BO. Like earlier authors, such as Helman et al.¹⁶ in their retrospective analysis of a cohort of 74 patients undertaken in 2012, we found length of the BO to be directly associated with severity of acid reflux. Therefore, as reported in studies published in 1998, there seems to be a clear association between the BO and the degree and length of acid exposure.¹⁷ This same association was found in both treatment groups. Although surgery is usually performed in patients with long-segment BO, our findings echo those of other studies that have shown that surgical treatment of short-segment BO results in improved control of acid reflux and mucosal healing.¹⁸ Some authors have suggested that patients with long-segment BO might be unusually resistant to PPIs. Although the underlying mechanism is not fully understood, this could explain the poor response to treatment shown by these patients. Reflux diathesis and delayed gastric emptying have been postulated as possible causes of this apparent resistance to the action of antacid drugs.⁹

In our experience, neither medical nor surgical treatment is entirely successful in controlling acid reflux measured by pH monitoring. A list of studies published to date (Table 3) shows the failure rate of these strategies. PPIs are the traditional, most widely used therapy in patients with severe to moderate symptoms of GORD. In most series, they are associated with poor control of acid reflux, with failure rates

Table 2 Inter-patient differences by length of Barrett's oesophagus.

	Long BO (n = 41)	Short BO (n = 87)	p
Age	47.24 ± 9.90	50.9 ± 11.52	0.262
Total number of refluxes >5 min	9.55 ± 8.16	4.78 ± 5.07	0.001
Total fraction of time with pH <4(%)	27.040 ± 111.42	7.568 ± 11.51	0.001
Upright	19.458 ± 65.32	7.560 ± 11.07	0.007
Supine	25.292 ± 57.23	10.737 ± 17.13	0.042
DeMeester	55.676 ± 82.44	34.628 ± 49.68	0.002
Anti-reflux surgery	n = 19 (46%)	n = 34 (39%)	0.27

Data shown as mean ± standard deviation.

Table 3 Principle studies on acid reflux control in BO.

	Year	Patients	Treatment	Parameter	Definition of failure	%failure
Hofstetter et al. ²²	2001	21	SI	pH (before and after SI)	Time pH <4 >4.4%	17%
Oelschlager et al. ²⁶	2003	53	SI	pH		23%
Gerson et al. ²⁷	2004	48	Single dose PPI (6%) Omeprazole 13 Lansoprazole 11 Rabeprazole 20 Esomeprazole 3 Pantoprazole 1	pH	Time pH <4 >5.5%	50%
Gerson et al. ²⁸	2005	17	PPI Rabeprazole 40 mg 11 Rabeprazole 20 mg 6	pH	Not defined	59%
Spechler et al. ⁹	2006	31	PPI Sequential Esomeprazole 40 mg and 20 mg	pH		16–23%
Mackalski et al. ¹⁹	2008	107 (GORD)	PPI Single dose/24 h 11 Double dose/12 h 15	pH	Time pH <4 >4.4%	24% (26)
Watson et al. ²⁰	2013	36	PPI	pH		22%
Parrilla et al. ²¹	2003	43	PPI	pH	Time pH <4 >5%	25%
		58	Omeprazole 20/12 h Ranitidine 150 mg/12 h SI			15%
LOTUS study ¹	2008	21	PPI Esomeprazole 40 mg/24 h	Symptoms	Questionnaires GSRS QOLRAD	10.7% 3.12%
Leon Hospital	2015	75	SI PPI	pH	Time pH <4 >5%	40%
		53	SI			13%

GSRS: Gastrointestinal Symptom Rating Scale; PPI: Proton pump inhibitors; QOLRAD: Quality of Life in Reflux and Dyspepsia; SI: Surgical intervention.

ranging from 20% to 40%. Earlier studies show slightly lower rates, such as the 16.23% failure rate reported by Spechler et al. in 2006. In another series of 107 patients published in 2008, with a similar definition of therapeutic failure to ours, acid reflux remained uncontrolled in 24% of patients.¹⁹ These findings are similar to others obtained from a study of 36 patients by Watson et al.,^{19,20} in which pH control was poor in 22% of patients. In our group, up to 40% of patients presented pathological acid reflux, despite PPIs. One explanation for this is that we collected data retrospectively from patient records in the pH monitoring database, aware of the fact that patients receiving PPIs undergo pH monitoring because of the refractory nature of their symptoms. These patients, therefore, are most likely to present poor acid reflux control. Although the aim of our study was not to analyse prolonged use of PPIs, it is important to note that this therapy has been recommended for the chemoprevention of OAC.⁴

Surgery (laparoscopic Nissen fundoplication) is the standard treatment when PPIs fail. This strategy, however, has fallen out of favour in recent years due to the high rate of relapse, which forces patients to fall back on PPIs, with all their associated side effects, the most common of which is dysphagia. This is reflected in our findings; although acid reflux control improved with surgery, post-surgery relapse, though minimal, was nevertheless around 15%. This is similar to the results reported by Parrilla et al.²¹:

postoperative functional studies showed that fundoplication restored the competence of the lower oesophageal sphincter and reduced acid reflux in 85% of the 58 cases analysed. Similar long-term results were found in the LOTUS (2008) study: after 3 years of follow-up, acid reflux control was significantly better following laparoscopic surgery vs PPI therapy (esomeprazole).¹ Table 3 summarises the results of the most important studies in acid reflux control using either of these 2 therapeutic options, together with the findings from our study.

The outcome is even better when pH monitoring parameters are compared before and after surgical intervention. In the subgroup of 19 patients, 95% presented good acid reflux control (less than 5% of time with pH <4). This is similar to the outcome reported by Hofstetter et al.,²² where a pre- and postoperative analysis of pH levels showed significant improvement in time with pH <4 in 83% of 21 patients analysed.

Our study has a few weak points, perhaps the most important being its retrospective nature, which exposes us to patient selection bias. Moreover, patient selection, being retrospective, was more prone to loss of data, such as diagnosis and the type, regimen and dosage of PPIs in the medical treatment arm. These data would have helped clarify which regimen and dosage of each type of PPI is needed to control acid reflux in BO. We did not evaluate the presence or absence of symptoms when performing pH monitoring,

because this information was not noted in our records. This prevented us from evaluating the observations made by other authors, namely, that symptoms do not correlate with objective measurement of pathological acid reflux. Unlike recent studies, we did not evaluate whether surgical treatment facilitated regression of BO and/or dysplasia. The controversy surrounding this issue is illustrated by the systematic review published by Chang et al.,²³ who were unable to show that anti-reflux surgery was more successful than medical treatment in preventing OAC, despite reviewing 25 papers. Our results are consistent with those of previous studies, however, and show that surgery is more successful in controlling acid reflux. Nevertheless, the lack of randomisation in our study prevents us from ruling out selection bias, insofar as patients with the severest symptoms are those that receive treatment, and are therefore those that most benefit from surgery.

To conclude, medical treatment must be optimised, compliance with PPI therapy and determination of dosage must be investigated, and response to treatment monitored. Despite the broad range of therapeutic options currently available, acid reflux control in patients with BO is still far from optimal. Fundoplication is the best treatment to control acid reflux; however, it is not without its complications, and effectiveness depends on the level of experience in each hospital. It is important to explain to patients the benefits and drawbacks of each therapeutic approach so that they can share in the decision-making process.

A number of promising surgical and endoscopic techniques, such as transoral fundoplication (EsophyX), are currently being developed for the treatment of GORD and BO.^{24,25} Further studies are needed to compare long-term outcomes with these and other techniques available today.

Conflict of interests

The authors declare they have no conflicts of interest.

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