Systematic review

Systematic review of endoscopic treatments for gastro-oesophageal reflux disease

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Background: **The aim of this review was to assess the safety and efficacy of endoscopic procedures for gastro-oesophageal reflux disease.**

Methods: **Literature databases including Medline, Embase and PubMed were searched up to May 2006 without language restriction. Randomized controlled trials and non-randomized comparative studies with at least ten patients in each study arm, and case series studies of at least ten patients, were included.**

Results: **A total of 33 studies examining seven endoscopic procedures (Stretta® procedure, Bard® EndoCinch™, Wilson-Cook Endoscopic Suturing Device, NDO Plicator™, Enteryx®, Gatekeeper™ Reflux Repair System and Plexiglas®) were included in the review. Of the three procedures that were tested against sham controls (Stretta® procedure, Bard® EndoCinch™ and Enteryx®), patient outcomes in the treatment group were either as good as, or significantly better than, those of control patients in terms of heartburn symptoms, quality of life and medication usage. However, for the two procedures that were tested against laparoscopic fundoplication (Stretta® procedure and Bard® EndoCinch™), outcomes for patients in the endoscopic group were either as good as, or inferior to, those for the laparoscopic group.**

Conclusion: **At present there is insufficient evidence to determine the safety and efficacy of endoscopic procedures for gastro-oesophageal reflux disease, particularly in the long term.**

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Introduction

Gastro-oesophageal reflux disease (GORD) is a chronic condition involving the spontaneous and involuntary reflux of stomach contents into the oesophagus because of an incompetent lower oesophageal sphincter (LOS). GORD causes a burning sensation in the chest or throat, and the long-term possible sequelae of chronic acid exposure to the oesophageal mucosa include ulceration, Barrett's oesophagus and oesophageal cancer. Obesity, smoking and alcohol consumption are thought to be risk factors for GORD.

The prevalence of GORD in Western countries ranges between 10 and 20 per cent[1]. In the USA, approximately 18·6 million patients with GORD are treated annually, with direct costs approximating US $9·3 billion, and antireflux medications accounting for US $5·8 billion of this[2]. In Australia, between 1999 and 2000, approximately three million prescriptions for proton pump inhibitors, the mainstay of medical treatment, were dispensed at a cost of AU $270 million[3].

The treatment of GORD depends on both symptom severity and individual patient characteristics. Conservative treatment may involve lifestyle changes such as weight loss, smoking cessation, and limiting meal sizes and alcohol intake[4]. Drugs such as proton pump inhibitors are introduced if symptoms persist despite lifestyle changes, but the inconvenience and cost of long-term daily medication can lead to non-compliance. Surgery in the form of fundoplication is indicated when the above measures fail, or at the patient's request. Fundoplication was previously performed via a thoracotomy or laparotomy, but this has since been superseded by a laparoscopic approach. While laparoscopic fundoplication is the 'gold standard' for the surgical treatment of GORD,

its inherent invasive nature as a surgical procedure remains.

In response to the inconvenience and non-compliance associated with drug use, and the complications associated with laparoscopic operation, a number of endoscopic techniques have been developed to treat GORD[5]. These procedures target the LOS and aim to improve function and reduce oesophageal acid exposure. In addition, preservation of the gastro-oesophageal junction (GOJ) allows for the possibility of future surgical therapies. Endoscopic techniques are performed as outpatient procedures, resulting in reduced operating theatre and other costs[5,6].

Endoscopic antireflux techniques can be divided into three broad categories. First, there are thermal ablation techniques, such as the Stretta® procedure (Curon Medical, Fremont, California, USA), which aims to narrow the oesophagus at the LOS by applying heat to the mucosal layer at the LOS directly above the GOJ. Second, there are suturing techniques using devices such as the Bard® EndoCinch™ (C. R. Bard, Murray Hill, New Jersey, USA), the Wilson-Cook Endoscopic Suturing Device (Wilson-Cook Medical, Winston-Salem, North Carolina, USA) and the NDO Plicator™ (NDO Surgical, Mansfield, Massachusetts, USA), which attempt to create a plication at the level of the LOS. Finally, there are injection or implantation techniques using, for example, Enteryx® (Boston Scientific, Natick, Massachusetts, USA), the Gatekeeper™ Reflux Repair System (Medtronic, Minneapolis, Minnesota, USA) and Plexiglas®, which aim to bulk up the LOS by injecting inert biopolymers into the muscularis layer of the oesophagus.

The aim of this review is to assess the safety and efficacy of these endoscopic procedures for the treatment of GORD.

Methods

Literature search strategies

A search was conducted of Medline, Embase, Cinahl, PubMed, The Cochrane Library, Science Citation Index, The York Centre for Reviews and Dissemination, Clinicaltrials.gov and the National Research Register, from the inception of the databases up to May 2006. The search terms used were as follows: gastroesophageal reflux disease, gastrooesophageal reflux disease, gastro-oesophageal reflux disease, GORD, GERD, stretta, bard endocinch, Wilson-cook device, enteryx implant, NDO plicat*, gatekeeper reflux repair system, plexiglas implant*, endoscopic treatment*, endoluminal gastroplicat*, radiofrequency energy application, endoscopic luminal gastroplasty, biopolymer augmentation therapy, full thickness plicat*, polymethylmethacrylate, ethylene vinyl alcohol copolymer, polyacrylonitrile, laparoscopic nissen fundoplication and proton pump inhibitor.

Inclusion criteria

Articles were retrieved when they were judged possibly to meet the inclusion criteria. Randomized controlled trials (RCTs) and non-randomized comparative studies with at least ten patients in each study arm and case series studies of at least ten patients were included in the review if they reported safety and efficacy outcomes for the endoscopic procedures listed above. Conference abstracts were included if they contained relevant safety and efficacy data. Two reviewers independently applied the inclusion criteria and any differences were resolved through discussion. Included studies were assigned a level of evidence according to the National Health and Medical Research Council hierarchy of evidence (*Table 1*)[7], and all comparative studies were critically appraised for study quality according to the guidelines in the Cochrane reviewer's handbook[8].

Data extraction and synthesis

Data were extracted by one researcher and checked by a second using standardized data extraction tables that were developed *a priori*. Data were reported only if stated in the text, tables, graphs or figures of the articles.

Table 1 National Health and Medical Research Council hierarchy of evidence (2000)[7]

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomized controlled trials
II	Evidence obtained from at least one properly designed randomized controlled trial
III-1	Evidence obtained from well designed pseudorandomized controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomized, cohort studies, case–control studies or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pretest/post-test

Results

The initial searches identified 57 studies; however, 23 were excluded because they duplicated data presented in other studies, had fewer than ten patients in the study arm or did not report safety outcomes (*Fig. 1*). In the end, a total of 33 studies were included in the review, including four RCTs, four non-randomized comparative studies and 25 case series (*Table 2*).

Safety

No procedure-related deaths were reported in any of the studies.

Stretta® procedure

An RCT reported that in the Stretta® group one patient (3 per cent) experienced bloating and another (3 per cent) oesophageal ulceration, and after the sham procedure one patient (3 per cent) developed pneumonia[9]. One non-randomized comparative study reported that in the Stretta® group one patient (2 per cent) had gastroparesis, and patients who had the laparoscopic operation had complications such as enterotomy (3 per cent), pneumothorax (1 per cent), paraoesophageal hernia (1 per cent) and incisional hernia (3 per cent)[2]. The most common complications reported in case series studies included transient epigastric pain (66 per cent) or chest pain (median 15 (range 2–100) per cent), low-grade fever (median 7 (range 2–13) per cent), superficial mucosal tears (median 4 (range 3–6) per cent), oesophageal ulceration (4 per cent) and dysphagia or odynophagia (median 3 (range 1–78) per cent)[10–19].

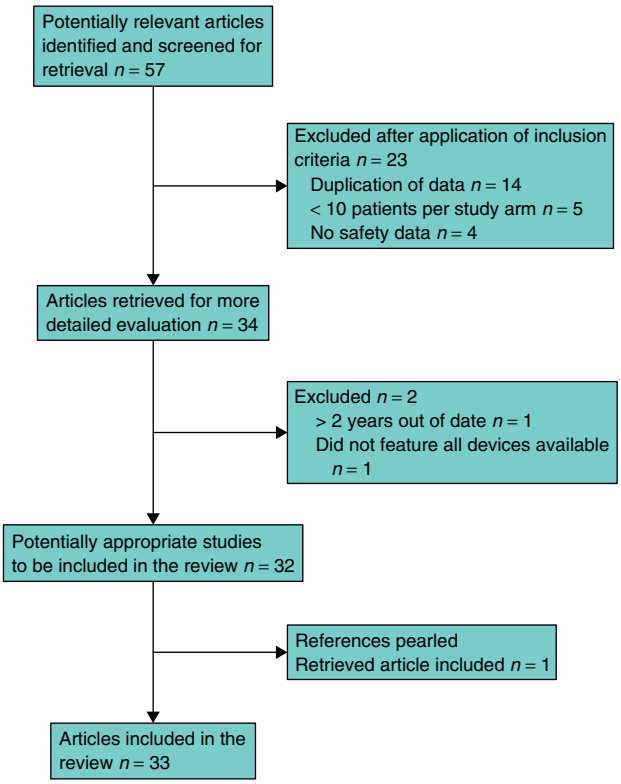

Fig. 1 Summary of the literature search and exclusion process. If a reference was 'pearled', it was obtained through manual searching of the retrieved articles

Bard® EndoCinch™

Two comparative studies have outlined complication rates[22,23]. One reported that, within 24 h of treatment, patients who had EndoCinch™ therapy had hypoxia (13 per cent), aspiration (4 per cent), bleeding (2 per cent), pharyngitis (57 per cent), nausea and vomiting (4 per cent) and a mucosal tear (2 per cent)[22]. In contrast, patients who had laparoscopic operation had pneumothorax (3 per cent), urinary retention (3 per cent) and severe nausea and vomiting (8 per cent) within 24 h of treatment, with further complications such as chest pain (30 per cent) and dysphagia (51 per cent) occurring after 24 h[22]. Mahmood and colleagues[23] reported that following the EndoCinch™ procedure three patients had bleeding (11 per cent) and one patient suffered a gastric mucosal tear (4 per cent), whereas patients who had laparoscopic fundoplication had dysphagia (17 per cent) and difficulty vomiting (25 per cent) and belching (41 per cent). In case series studies, common complications following the procedure included pharyngitis (31 per cent), transient chest pain (median 15 (range 3–83) per cent), nausea and vomiting (median 16 (range 3–18) per cent), abdominal pain (14 per cent), dysphagia or odynophagia (median 5 (range 1–18) per cent) and bleeding (median 5 (range 3–11) per cent)[25–31].

Wilson-Cook Endoscopic Suturing Device

In two case series, this procedure was associated with transient chest pain, abdominal pain, nausea and self-limiting bleeding, with rates of these complications similar to those observed for EndoCinch™[32,33].

NDO Plicator™

A case series of seven patients reported that following the procedure two patients suffered mild mid-epigastric pain which resolved spontaneously within a week, and all patients were free from complications at 3 and 6 months' follow-up[34]. One case series of 64 patients reported a number of minor adverse events following plication, including pharyngitis (41 per cent), abdominal

Table 2 Summary of included studies

Study	Level of evidence	Study type	No. of patients	Outcomes	Length of follow-up (months)
Stretta® procedure					
Corley *et al.*[9]	II	RCT	Sham 29, Stretta® 35	Safety + efficacy	12
Richards *et al.*[2]	III-2	NRC	LF 75, Stretta® 65	Safety + efficacy	LF 5·2, Stretta® 7·3
Cipolletta *et al.*[10]	IV	PCS	32	Safety	12
DiBaise *et al.*[11]	IV	PCS	18	Safety	6
Go *et al.*[12]	IV	PCS	50	Safety	10
Lutfi *et al.*[13]	IV	PCS	77	Safety	26·2
Mansell[14]	IV	CS	29	Safety	4·5
Meier *et al.*[15]	IV	CS	40	Safety	12
Noar and Smith[16]	IV	CS	202	Safety	24
Reymunde *et al.*[17]	IV	Retrospective CS	50	Safety	31·7
Tam *et al.*[18]	IV	PCS	20	Safety	12
Triadafilopoulos *et al.*[19]	IV	PCS	118	Safety	12
Bard® EndoCinch™					
Rothstein *et al.*[20]	II	RCT	Sham 17, EndoCinch™ 17	Safety + efficacy	3
Domagk *et al.*[21]	II	RCT	Enteryx® 23, EndoCinch™ 26	Safety + efficacy	6
Chadalavada *et al.*[22]	III-2	NRC	LF 40, EndoCinch™ 47	Safety + efficacy	LF 7·3, EndoCinch™ 8
Mahmood *et al.*[23]	III-2	NRC	LF 24, EndoCinch™ 27	Safety + efficacy	12
Velanovich *et al.*[24]	III-3	NRC	LF 27, EndoCinch™ 27	Safety + efficacy	1·5
Abou-Rebyeh *et al.*[25]	IV	PCS	38	Safety	12
Arts *et al.*[26]	IV	PCS	20	Safety	12
Chen *et al.*[27]	IV	CS	85	Safety	24
Filipi *et al.*[28]	IV	PCS	64	Safety	6
Ponchon *et al.*[29]	IV	PCS	60	Safety	12
Schiefke *et al.*[30]	IV	PCS	70	Safety	18
Thomson *et al.*[31]	IV	PCS	17	Safety	23
Wilson-Cook Endoscopic Suturing Device					
Liu *et al.*[32]	IV	CS	10	Safety + efficacy	3
Schiefke *et al.*[33]	IV	PCS	20	Safety + efficacy	6
NDO Plicator™					
Chuttani *et al.*[34]	IV	PCS	7	Safety + efficacy	12
Pleskow *et al.*[35]	IV	PCS	64	Safety + efficacy	6
Enteryx®					
Devière *et al.*[36]	II	Single-blind RCT	Sham 32, Enteryx® 32	Safety + efficacy	6
Cohen *et al.*[37]	IV	PCS	144	Safety	24
Schumacher *et al.*[38]	IV	PCS	93	Safety	12
Gatekeeper™ Reflux Repair System					
Fockens[39]	IV	PCS	69	Safety + efficacy	6
Gabrielli *et al.*[40]	IV	PCS	13	Safety + efficacy	24
Plexiglas®					
Feretis *et al.*[41]	IV	PCS	10	Safety + efficacy	7·2

RCT, randomized controlled trial; NRC, non-randomized comparative; LF, laparoscopic fundoplication; PCS, prospective case series; CS, case series.

pain (20 per cent), chest pain (17 per cent), gastrointestinal disorder (17 per cent), eructation (14 per cent), dysphagia (11 per cent) and nausea (6 per cent), all of which resolved spontaneously[35]. Serious adverse events, including dyspnoea, pneumothorax, pneumoperitoneum, gastric perforation and mucosal abrasion in the fundus, occurred in six patients[35].

Enteryx®

One RCT reported that, at 3 months' follow-up, 69 per cent of patients in the Enteryx® group experienced retrosternal, chest or epigastric pain, 28 per cent suffered from dysphagia or odynophagia, and 3 per cent had bloating or flatulence, compared with 6, 9 and 3 per cent respectively in the control group[36]. By 6 months' follow-up, the cumulative incidence rates for these adverse events were similar in both groups. Similar rates of these adverse events were reported in two case series[37,38].

Gatekeeper™ Reflux Repair System

A case series of 69 patients[39], supplemented with additional data for 13 patients from a conference abstract[40], reported an overall complication rate of 15 per cent within 30 days of the procedure. Two patients had a serious

adverse event that required hospitalization, one had a pharyngeal perforation during the procedure and another postprandial nausea 1 week after the procedure. However, most complications were minor and required little or no intervention[39].

Plexiglas®

In one case series of ten patients, no serious complications were reported[41]. Two patients experienced chest pain which resolved within 2 days, one had minor self-limiting bleeding, and one complained of minor transient dysphagia as well as gas and bloating, which lasted 3 weeks.

Efficacy

Stretta® procedure

Corley and co-workers[9] demonstrated that patients undergoing the Stretta® procedure had significantly better heartburn ($P = 0{\cdot}010$) and quality of life (QOL) ($P = 0{\cdot}050$) scores than those in the control group at 6 months. GORD health-related quality of life (GORD-HRQL) scores were significantly better in the Stretta® group at 6 and 12 months ($P = 0{\cdot}003$) than in the control group. However, no difference was observed for oesophageal acid exposure time, LOS pressure or daily use of proton pump inhibitors.

A non-randomized comparative study reported that, at 6 months' follow-up, patients who underwent the Stretta® procedure had a significant improvement in oesophageal acid exposure time ($P < 0{\cdot}010$) and DeMeester acid scores ($P < 0{\cdot}010$) from baseline; however, no significant change was observed for LOS pressure[2]. No differences were observed between the Stretta® procedure and laparoscopic fundoplication with regard to QOL in reflux and dyspepsia (QOLRAD) and general QOL scores, but 97 per cent of patients no longer needed proton pump inhibitors following laparoscopic surgery compared with 58 per cent of patients who had the Stretta® procedure.

Bard® EndoCinch™

One RCT reported that at 3 months' follow-up there was a significant reduction in heartburn frequency ($P = 0{\cdot}049$), oesophageal acid exposure time ($P = 0{\cdot}013$) and daily use of acid-suppressing medication ($P = 0{\cdot}012$) in the EndoCinch™ group compared with the control group; however, LOS pressure was not significantly different between the groups[20]. Another RCT comparing EndoCinch™ with Enteryx® failed to demonstrate significant differences between the groups in terms of oesophageal acid exposure time, symptom scores and use of proton pump inhibitors at 6 months[21].

Two studies have shown that proton pump inhibitor usage is higher after EndoCinch™ treatment than after laparoscopic repair[22,23]. One non-randomized comparative study reported that, at 6 and 12 months, the degree of improvement in heartburn symptom score was significantly better in laparoscopically treated patients than in those who had EndoCinch™ ($P < 0{\cdot}050$)[23]. In addition, DeMeester acid scores ($P < 0{\cdot}001$) and oesophageal acid exposure time ($P < 0{\cdot}001$) were significantly better after laparoscopic surgery than after EndoCinch™ treatment; and 91 per cent of the former group achieved a normal oesophageal pH at 3 months compared with 48 per cent of the latter. Velanovich and colleagues[24] observed no significant difference between the two groups in terms of GORD-HRQL symptom improvement.

Wilson-Cook Endoscopic Suturing Device

In one case series of ten patients, an improvement in regurgitation frequency scores ($P < 0{\cdot}010$) and reflux symptoms was observed 3 months after treatment. However, LOS pressure and DeMeester acid scores did not change significantly[32]. Similarly, another case series reported an improvement in heartburn severity scores 6 months after treatment ($P < 0{\cdot}050$), with no significant changes in LOS pressure, QOL scores or use of proton pump inhibitors[33].

NDO Plicator™

One case series of seven patients reported that, a year after treatment, GORD-HRQL scores had improved by approximately 75 per cent, and that three of the five patients who were followed up were taking no medication for their reflux symptoms[34]. Another case series reported that, 6 months after plication, median GORD-HRQL scores had improved 67 per cent ($P < 0{\cdot}001$), the median oesophageal acid exposure time had improved 29 per cent ($P < 0{\cdot}008$) and 74 per cent of patients had stopped using proton pump inhibitors[35].

Enteryx®

An RCT involving 64 patients reported that, at 3 months' follow-up, the GORD-HRQL heartburn score in the Enteryx® group significantly improved by a median of 63 per cent from baseline, compared with 25 per cent in the control group[36]. At 3 months, Short Form 36 physical and mental QOL scores had improved significantly in patients having Enteryx® (median 14 and 16 per cent respectively) but not in control patients, although by 6 months scores had improved in both the Enteryx® (18 and 12 per cent respectively) and control (22 and 8 per cent respectively) groups. No significant difference in oesophageal acid exposure time was observed between the two groups, but

the rate of complete cessation of medication at 3 months was higher in the Enteryx® group (68 per cent) than in the control group (41 per cent) ($P = 0{\cdot}033$). At 3 months, significantly fewer patients having Enteryx® (19 per cent) had repeat treatment than control patients (81 per cent) ($P < 0{\cdot}001$).

Gatekeeper™ Reflux Repair System

Fockens[39] reported a significant improvement in median heartburn ($P < 0{\cdot}050$), regurgitation ($P < 0{\cdot}050$) and QOL (Short Form 36: physical) ($P < 0{\cdot}050$) scores, and median LOS pressure ($P < 0{\cdot}010$), at 6 months. After treatment there was a reduction in oesophageal acid exposure time ($P < 0{\cdot}050$) and 53 per cent of patients did not require proton pump inhibitors. However, pH had normalized in only 40 per cent of patients. The retention rate for the prosthesis at 6 months' follow-up was 70 per cent.

Plexiglas®

One case series demonstrated a significant improvement in mean symptom severity ($P = 0{\cdot}005$) and DeMeester acid ($P = 0{\cdot}005$) scores, and mean oesophageal acid exposure time ($P = 0{\cdot}007$), at follow-up (mean 7·2 months)[41]. However, oesophageal pH did not normalize in any of the ten patients, although 70 per cent did not require proton pump inhibitors.

Discussion

A total of 33 studies were identified that examined seven endoscopic procedures. Those tested against sham procedures achieved patient outcomes as good as or significantly better than the control group in terms of heartburn symptoms, QOL and medication usage. However, those tested against laparoscopic fundoplication produced patient outcomes only as good as, or inferior to, laparoscopic surgery.

Given the relatively recent introduction of endoscopic approaches for the management of GORD, it is not surprising that the number of published studies on each of these procedures is rather small. There is a little evidence to suggest that, in the short term at least, the Stretta® procedure can produce improvements in symptoms and QOL similar to those expected from laparoscopic fundoplication. Interestingly, these results did not show any correlation with reduced oesophageal acid exposure or an equivalent reduction in proton pump inhibitor usage, which raises the possibility that these improvements are due to a placebo effect. Furthermore, an additional intervention is required in up to 10 per cent of patients 2 years after treatment, compared with 1 per cent after laparoscopic surgery[2]. Although the Stretta® procedure is less invasive than a laparoscopic operation, is associated with fewer serious complications and can be performed on a day-case basis under sedation, the fact that it does not alter oesophageal acid exposure suggests a limited, if any, role for it in the treatment of GORD. While the Stretta® was the most widely implemented endoscopic procedure for GORD, the device has not been available since 2006, when Curon Medical, the company that marketed it, ceased operations.

When the Bard® EndoCinch™ was compared with sham treatment, symptom relief appeared similar in both groups after 3 months, except for a significant improvement in heartburn frequency observed in the treatment group that correlated with a reduction in oesophageal acid exposure and medication usage[20]. When compared with laparoscopic fundoplication, the EndoCinch™ provided similar or slightly inferior results in terms of medication usage and symptom relief [22–24]. Although the procedure has been shown to be safe, it has been associated with a reintervention rate of up to 55 per cent within 2 years[26].

The NDO Plicator™ has been shown to have a positive effect on reflux symptoms, oesophageal acid exposure, medication usage and QOL in two small case series[34,35]. However, well designed RCTs are needed to determine the efficacy of this procedure.

Enteryx® implantation has been shown to improve symptoms and reduce medication usage compared with sham treatment, but it is associated with a reintervention rate of up to 25 per cent within 2 years[36]. Although the studies in this review reported only minor complications following implantation, Enteryx® was voluntarily recalled by the manufacturer in 2005, after reports of serious adverse events and deaths, which were associated with its use outside of a clinical trial setting.

The Gatekeeper™ Reflux Repair System has been shown in one case series to improve symptoms, QOL, LOS pressure, oesophageal acid exposure and medication usage 6 months after treatment[39]. However, the retention rate of the implant was only 70 per cent at 6 months, and up to 15 per cent of patients required retreatment within 6 weeks of the initial procedure. This device is no longer being marketed.

GORD has been shown to have a placebo response rate of up to 50 per cent, as shown by results from sham control studies[42,43]. However, subjective improvements in outcomes such as symptoms and QOL may not necessarily correlate with objective measures such as oesophageal acid exposure, and debate continues over the mode of action of various endoscopic therapies. Wenzel and co-workers[44]

have suggested that the inadvertent injury of submucosal sensory fibres from the vagus nerve may lead to falsely improved subjective outcomes. If so, this may potentiate the undetected effects of acid reflux, which may have serious sequelae[42,43].

Because of their minimally invasive nature, endoscopic procedures are associated with shorter operative and recovery times than laparoscopic surgery, which presents an avenue for cost saving. However, this cost saving may be offset by the expense of equipment and the possible need for reintervention. In order for endoscopic procedures to be more cost-effective than surgery, they need to achieve long-term efficacy combined with low failure rates. However, the results from decision analysis models indicate that retreatment rates for Stretta®, EndoCinch™ and Enteryx® are currently too high to achieve this[44].

The learning curves for these procedures have not been well defined; some procedures require more training than others. Endoscopic suturing of the LOS appears to be the most technically demanding[45], while the Stretta® procedure is less demanding, with no apparent difference in outcomes between physicians who have performed at least ten procedures and those who have not[2]. Although such interventions can be undertaken safely within the confines of a clinical trial, it is essential that specific training requirements are clearly defined before the procedures are introduced into routine clinical practice.

Overview

The number of patients worldwide who are taking proton pump inhibitors suggests that there is a need for endoscopic procedures, especially in patients with mild to moderate GORD who are dependent on medication but are reluctant or unable to undergo surgery. However, despite the potential benefits of these procedures, there is insufficient evidence at present to establish their safety and efficacy, particularly in the long term. Their widespread use in the future will depend, first, on improvements in the techniques themselves and, second, on the emergence of high-quality data to demonstrate their long-term safety and efficacy. Clearly, there is a need for RCTs to compare endoscopic procedures with the currently accepted treatments for GORD, namely drug therapy and laparoscopic fundoplication. As there is evidence to suggest that the observed benefits associated with some endoscopic procedures may be due to a placebo effect, it is important that future RCTs examine whether subjective measures of improvement, such as drug usage and QOL scores, are supported by objective measures, such as oesophageal acid exposure.

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