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Article *in* Alimentary Pharmacology & Therapeutics · April 2008

DOI: 10.1111/j.1365-2036.2007.03593.x · Source: PubMed

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Review article: endoscopic antireflux procedures — an unfulfilled promise?

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Publication data
Submitted 16 November 2007
First decision 29 November 2007
Resubmitted 7 December 2007
Second decision 9 December 2007
Resubmitted 10 December 2007
Accepted 16 December 2007
Epub OnlineAccepted 20 December 2007

SUMMARY

Background
Most published reviews concerning the endoscopic treatment of gastro-oesophageal reflux disease date back to 2005.

Aim
To provide an updated review that includes all papers published up to 2007.

Methods
A Medline search from January 2005 to June 2007 was performed regarding endoscopic procedures aiming at treating gastro-oesophageal reflux disease. In addition, we retrieved the abstracts presented at Digestive Disease Week during the last 3 years. We included in the review both 'mechanistic' studies – that is, papers exploring the potential mechanism of action of the procedure/device – and studies trying to assess its clinical efficacy.

Results
During the last 3 years, the number of published papers has declined, and some devices are not available any more. The alleged mechanism(s) of action of the various devices or procedures is (are) still not completely elucidated; however, some concerns have arisen as far as durability and potential detrimental effects. Moreover, all the aspects of endoscopic therapy, except for its safety, are either insufficiently explored or not investigated at all, or assessed only in particularly selected patient subgroups.

Conclusions
None of the proposed antireflux therapies has fulfilled the criteria of efficacy, safety, cost, durability and, possibly, of reversibility. There is at present no definite indication for endoscopic therapy of gastro-oesophageal reflux disease. We suggest a list of recommendations to be followed when a new endoscopic therapeutic procedure is to be assessed for use in clinical practice.

doi:10.1111/j.1365-2036.2007.03593.x

INTRODUCTION

The chronic nature of gastro-oesophageal reflux disease (GERD) and the frequent need for long-term treatment have become increasingly apparent in the past 15 years.[1] Acid suppression, in particular achieved by proton pump inhibitors (PPIs), is an effective therapy in most patients, although it does not address the main abnormality: the impaired function of the lower oesophageal sphincter.[1] Surgical fundoplication has shown to be an effective and durable option for control of GERD symptoms.[2, 3] Its appeal has increased since the introduction of minimally invasive techniques. Nevertheless, the benefit should be balanced against the reported 0.5–1% risk of mortality,[4] the experience of the surgeon[5] and a possible decline of efficacy overtime[3, 6]

These caveats have fueled the interest for endoscopic antireflux procedures (EARPs) in the last decade. Following the pioneer experience of the group of Swain[7] with an endoluminal sewing device, three different approaches have been carried out: endoscopic suturing, intraluminal radio-frequency delivering and injection of bulking agents in the muscle layers of the lower oesophagus. More technical details on these procedures are presented in the following sections. However, what is peculiar for all these devices has been the prompt delivering on the market based on few preliminary data on safety and clinical efficacy, without any controlled trial. This has become possible because of the profound difference of requirements between device and drugs adopted by regulatory agencies like Food and Drug Administration (FDA) and European Agency for Medicinals Evaluation. Whereas pharmaceuticals undergo wide scrutiny and subsequent marketing practices, medical devices are regulated under a risk-based system. Devices with a low-moderate risk (as the endoscopic devices were classified) enter the market through a process requiring only supporting data of 'equivalence' to an existing device or procedure. In the case of radiofrequency device, (Stretta, Curon Medical Inc., Sunnyvale, CA, USA) for example, the accepted evidence of FDA was an open-label study involving 47 patients,[8] demonstrating shorter hospital stay and recovery time compared with that in published data on fundoplication. Subsequent events (i.e. some deaths potentially associated with the use of Enteryx [Boston Scientific Inc., Natick, MA, USA] and Stretta)[9] have overcome the enthusiasm to the point that one device has been voluntarily withdrawn (Enteryx) and two others are no longer marketed (Wilson-Cook's ESD, Cook Medical, Inc., Bloomington, IN, USA and Medtronic's Gatekeeper, Medtronic Inc., Minneapolis, MN, USA) by the relative companies. Three others are still available [Stretta, EndoCinch (Bard Inc., Billerica, MA, USA), and the Plicator (NDO Surgical Inc., Mansfield, MA, USA)], although it appears that their sales in the 2006 were decreasing compared with 2005.[10] These considerations have reinforced the claim of many authors that data in support of the endoscopic antireflux devices were not sufficient to merit their routine use outside the research setting.[11–14] Despite these considerations, a considerable number of recent studies have appeared in the Literature, and we aimed at updating already existing reviews[15–18] by adding those papers published between 2005 and 2007.

METHOD

A Medline search from January 2005 to June 2007 was performed for articles regarding endoscopic treatment of GERD. Data have been retrieved through MedLine Search and Digestive Disease Week (DDW) CDs with the search terms: *endoscopic suturing, endoscopic sewing, plication, gastroplication, Enteryx, EndoCinch, Plicator, Hiz-Wiz, ESD, Gatekeeper, Stretta, radiofrequency, ELGP (endoluminal gastroplasty)*. Besides this, just to give an idea of the trend in scientific productivity in this field, we counted the number of original papers published and abstracts accepted at the Digestive Disease Week for human studies in the last 5 years.

RESULTS

We will present the results of the survey in the following paragraphs dividing them into five sections: global considerations, studies exploring the mechanism of action and individual devices such as injection/implant therapy, endoscopic suturing, Stretta procedure. The methodology of each procedure is briefly recalled at the beginning of every section.

Global considerations

Along with the evolving data on the efficacy of EARPs,[15–18] there has been a change in interest and attraction of the scientific community for these devices. Figure 1 depicts the number of original papers

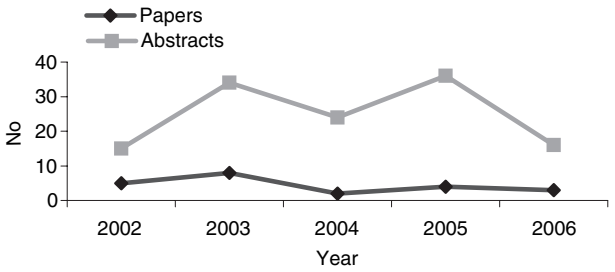

Figure 1. Number of published full articles or accepted abstracts at Digestive Disease Week in the last 5 years.

published and abstracts accepted at the Digestive Disease Week for human studies in the last 5 years.

Two aspects are clearly shown: first, a discrepancy between the number of abstracts and that of peer-reviewed papers. Second, a clear decline in the scientific production overtime. Accordingly, in the leading article on the 'past and future of gastrointestinal endoscopy', Sivak[19] claims that looking at major achievements of endoscopy in the last decade, the endoscopic treatment of GERD is conspicuously absent. The main reason is that the quality of trials available in the literature is limited. For example, at the time of writing, only three sham-controlled trials have been published,[20–22] and all suffer from substantial caveats. In these studies, a combination of subjective (i.e. symptom scores and medications use), and objective measures of GERD severity (i.e. pH-metry) has been used. Moreover, the patient unblinding hampers the positive findings achieved with the former, as all these procedures carried a significant increased rate of adverse events (i.e. chest and shoulder pain, garlicky breath), which would unmask the blindness to the majority of patients (and investigators). Furthermore, another issue of concern is the relatively short duration of these controlled trials (3–6 months), which make unwise to commit such therapeutic option to a young, otherwise healthy individual. Finally, perhaps the major drawback is that such studies do not compare the clinically relevant treatment strategies: acid suppression and surgery. As these devices are being marketed as alternatives to chronic PPI use, it would be logical to compare such devices with medical or surgical management. A controlled study of EndoCinch vs. Enteryx[23] and a prospective non-randomized comparison with fundoplication[24] do not further clarify the issue. In addition, the restriction to include in clinical trials only sub-groups of subjects with mild GERD (i.e. no patients with severe oesophagitis or Barrett's oesophagus) turns out to be a major flaw: accordingly, until now, we simply do not know the potential role of these device in the 'real world' of GERD.

Mechanism of action

Eleven studies were found addressing this issue.[25–35] The mechanism of action of suturing devices, also called devices for ELGP, remains unclear. A lower volume of refluxate reaching the 'more sensitive' proximal oesophagus can explain the symptomatic improvement, but this has not been formally investigated. The scar formation may reduce the distension capacity of proximal stomach, and decrease the frequency of transient lower oesophageal sphincter relaxations (tLESRs), but again no mechanistic studies are available. Moreover, the ELGP may increase the basal tone of the LES through a localized circular muscle hypertrophy,[25] and modify the compliance of the gastro-oesophageal (GE) junction.[26] When the serosa is incorporated in the plication (i.e. with the Plicator device), a higher degree of fibrosis is obtained and suture retention should improve.[27] Indeed, suture patency has been noted in long-term study with EndoCinch and Wilson-Cook's ESD.[28–30]

The radiofrequency delivery may produce multiple changes: first, a mechanical alteration because of a thickening of the LES musculature, as shown in the canine model.[31] Furthermore, the progressive tissue remodelling and scar formation could modify the compliance and tension strength at the GE junction. This may also represent the explanation of the observed reduction of tLESRs.[32] The discrepancy between symptomatic improvement and no significant decrease in acid exposure has also been explained through an effect of reduced visceral perception,[20] because of destruction of chemosensitive nerve endings.[33] This effect, although theoretically attractive in patients with 'irritable' oesophagus, could be potentially detrimental, leading for example to an 'asymptomatic' transformation to columnar lined epithelium.

The bulking implants lead to an increase in the yield volume and pressure because of fibrous encapsulation (Enteryx) or bulking effect (Gatekeeper, Plexiglas microspheres). A raised threshold for tLESRs has been demonstrated with Enteryx in a porcine model and in humans,[34, 35] whereas sloughing and migration of injected material may be the reasons for the lack of durability of these agents.

Table 1. Studies of injection therapy in patients with gastro-oesophageal reflux disease

First author (Ref.)	Year	Patients (*n*)	Device	Follow-up (months)	Patients off proton pump inhibitor (%)	pH < 4, pre/post (%)
Cohen[36]	2005	59	Enterix	24	67	10/6 (at 12 months)
Schumacher[37]	2005	93	Enterix	12	52	11/11
Domagk[23]	2006	51	Enterix vs. Endocinch	6	NA	15/10 (Endo-Cinch) 16/14 (Enteryx)
Deviere[21]	2005	64	Enterix	6	68	13/11 (Enteryx) 14/13 (Sham)
Fockens[38]	2004	69	Gatekeeper	6	53	9/6

Injection/implant therapy

Five recent studies were found by our search[21, 23, 36–38] (Table 1), which confirm drawbacks and inconsistencies concerning endoscopic injection therapies for GERD, which led to withdrawal from the market of Enteryx and GateKeeper. Despite initial symptomatic improvement reported by the majority of studies, gastric acid reflux is not significantly reduced or normalized and lower oesophageal sphincter pressures are not improved.

Cohen *et al.*[36] recruited an additional 59 patients to expand at 24-month follow-up on a previous published Enteryx multicentre trial.[39] This investigation provides evidence for sustained effectiveness and safety of Enteryx implantation in PPI-dependent patients with GERD. When applying an intent-to-treat analysis, this results in 78% of patients responding at 12 months. Improvement in GERD-HRQL symptoms, defined as a score ≤11, was achieved in 78% of patients, and PPI use stopped in 73%. At 12 months, oesophageal acid exposure declined significantly from a median of 10–6.4 ($P < 0.01$). There was no change in grade of oesophagitis in 55% of patients, while the grade improved in 13% and worsened in 32%. At 24 months, ≥50% or greater reduction in PPI use was achieved in 72%, and PPI use was eliminated in 67% of patients.

A second large-population, open-label study of 93 patients was recently published by Schumacher *et al.*[37] Using an intention-to-treat analysis, the primary end point (≥50% reduction in PPI use) was reached in 69%, and 52% terminated PPI use entirely. The authors reported a significant improvement in GERD-HRQL and SF-36 scores at 12 months when compared with pre-implantation. Interestingly, despite improvements in medication use and quality of life (QOL), there were no significant changes in pH-metry or oesophageal manometry.

Domagk *et al.*[23] recently compared, in a prospective, randomized trial, Enteryx with endoluminal gastroplasty (BARD EndoCinch) employing 51 patients. This study is of particular interest, as it is the only one assessing two different endoscopic procedures in a head-to-head comparison. At 6 months, PPI therapy could be stopped or dosage reduced by ≥50% in 20 of 26 (77%) EndoCinch-treated patients and in 20 of 23 patients treated by Enteryx™ (87%, $P = 0.365$); both groups post-operatively differed significantly compared to the pre-interventional status ($P < 0.0001$). Oesophageal acid reflux (pH < 4) decreased from 15% to 10% in EndoCinch-treated patients ($P = 0.071$) and from 16% to 14% in patients treated by Enteryx™ ($P = 0.930$). Heartburn symptom score, modified DeMeester score, gastrointestinal life quality index, and SF-36 score improved significantly in both groups post-interventionally ($P < 0.0001$). Approximately 25% of the patients in both groups required re-treatment in an attempt to achieve symptom control. In conclusion, both procedures seemed to be equally ineffective in normalizing underlying GER, although GERD symptoms, QOL and PPI consumption were ameliorated in both groups.

Devière *et al.*[21] reported the results of a randomized, prospective, multicentre, sham-controlled, 6-month cross-over trial conducted on 64 patients treated with Enteryx. At 3 months, 81% of the Enteryx group and 53% of the sham group achieved the primary endpoint (a 50% or greater decrease in PPI use). Secondary endpoints (a > 50% improvement in GERD HRQL and proportion of patients not requiring re-treatment) also favoured Enteryx use: 68% of those treated with Enteryx were off PPIs, compared with 40% sham. Although pH-monitoring was performed only in a

subgroup of treated patients, there was no significant improvement in pH data between treated and untreated patients.

Perhaps the most important recent Enteryx publications dealt with emerging safety concerns. Noh *et al.*[40] described a case of pneumo-mediastinum. This follows a previous report of a death because of uncontrollable upper gastrointestinal bleeding in an elderly female, in whom autopsy revealed an aorto-oesophageal fistula. It was postulated that a trans-oesophageal injection led to aortic necrosis and subsequent fistula formation.[41] Another death associated with Enteryx was because of para-oesophageal abscess.[42] Also, Wong *et al.*[43] reported two cases of mediastinal complications of Enteryx. On 23 September 2005, Boston Scientific Corporation initiated a voluntary recall of Enteryx. The manufacturer states that this action was not related to the safety and effectiveness of Enteryx when properly implanted and that there was no evidence of complications resulting from long-term implantation of Enteryx.[44]

Definitive and extensive data on Gatekeeper reflux repair system are still limited to the open-label multicentre trial published in 2004.[38] This work showed that after 6 months, 53% of patients were off PPI treatment, with a slight although significant increase in basal LES pressure and an improvement, but not a normalization of oesophageal acid exposure. As demonstrated by an interesting Italian study, endoscopic implant of hydrogel prostheses above the lower oesophageal sphincter significantly decreases proximal spread of acid reflux into oesophageal body,[45] allowing a promising involvement in the management of extra-oesophageal manifestations of GERD. However, the relapse rate because of spontaneous dislodgement of the microprostheses, as high as 30% after 6 months,[38] led the Company itself (Medtronic Inc., Minneapolis, MN, USA) to cut off manufacturing the device.

Endoscopic suturing

Following the initial enthusiasm towards, and subsequent failure of, injectable polymers and implants, manufacturing companies have now shifted their focus and are increasingly investing resources on suturing devices. This approach attempts to create a plication at the level of the cardia, producing a mechanical barrier to the reflux of gastric content. Three suturing devices have been marketed: Endocinch (Bard Inc., Billerica, MA, USA) which is both FDA approved and CE marked, Plicator (NDO Surgical Inc.) FDA approved since April 2003 and winner of the Medical Design Excellence Award in 2004, and EsophyX (EndoGastric Solutions, Redmond, WA, USA) CE marked since May 2006 and undergoing investigation for FDA approval.

The Endocinch procedure consists of 2 to 3 plications 1–2 cm below the GEJ, for a procedure time between 25 and 100 min.[28, 46, 47] Patients have been treated both under deep sedation and under conscious sedation.[46] Clinical evidence suggests that the primary shortcoming of the Bard device is that the plication is only anchored by the mucosal layer. The result is thus a weak valve that yields with pressure over time because of loss of sutures.[28]

The Plicator procedure consists of the placement of a single suture below the GEJ under direct visualization. Contrary to the Bard device, it is designed to create a full-thickness plication, and thus a longer lasting GE valve. Presumably, the failure in clinical efficacy may be attributable to the limitations of the single suture implant, which may be insufficient to create an effective antireflux barrier.

The already marketed EsophyX device aims at restoring the GE valve by means of a full-thickness, omega-shape fundoplication.[48] The procedure is performed under direct visualization, and lasts between 30 and 90 min. The technology is promising, and the preliminary clinical results have shown significant improvements in 24-h pH monitoring. Nevertheless, without a long-term clinical evaluation based on a larger patient population, the efficacy of the procedure is still to be assessed. A 1-year follow-up for the first 17 patients will be published shortly, and a multi-centre European clinical registry is currently under study.

One further device, still currently under investigation, is the Hiz-Wiz; a recent abstract has been published on the 1-year follow-up of the first seven patients treated.[49] The procedure consists of creating two plications, respectively anteriorly and posteriorly, just below the GE junction. The procedure is performed under sedation, and is reported to last approximately 5–10 min. Results at 1 year show an improvement in pH monitoring, but an inconsistent effect on symptoms.[49]

As for the safety of all these devices, reported adverse events included some minor ones such as abdominal and epigastric pain, vomiting, dysphagia, bloating, all resolving within the first days post-procedures, but also some serious adverse events, such as

gastric mucosal tear, pneumoperitoneum, gastric perforation and bleeding, which, however, resolved without long-term adverse outcomes.[50, 51]

An overview of the four recently published studies[28, 46, 48, 51] is given in Table 2.

Surprisingly, the primary end points of these studies have been QOL and PPI discontinuation. However, improvements in QOL scores are not directly correlated with improvements in pH monitoring[28, 46, 50, 51] and PPI withdrawal cannot be considered a reliable efficacy parameter. Furthermore, a consistent normalization of oesophageal acid exposure has not been shown by any of these techniques. The study published by Rothstein *et al.*[51] shows that 26% of patients in the sham cohort completely interrupted PPI medication at 3 months, while no significant difference was detected in the final grade of oesophagitis between the treatment group (34%) and the sham group (41%). Similarly, Schwartz *et al.*[46] comment that, although 65% of patients reported an improvement in medication use ≥50% at 3 months, no significant change in acid exposure was observed compared with the sham group.

Two further devices are currently under investigation: the MediGus SRS™ device (Omer, Israel) CE marked since May 2006, and the Syntheon ARD™ plicator (Miami, FL, USA), currently undergoing FDA review. The former device creates a partial anterior fundoplication of 120–180° by inserting surgical staples in proximity of the GEJ. The latter device creates a full thickness plication by placing a titanium implant at the level of the cardia. No clinical trials are available with either devices.

STRETTA procedure

As the publication of our and others reviews of the literature[15–18], four full papers[52–55] and a few abstracts[56–61] have reported uncontrolled results concerning the Stretta procedure in the medium/long term (i.e. ≥12 months for most of the patients) or its mechanism(s) of action, and they are shown in Table 3.

Full papers, two of which[53, 54] deal with the same series, have concluded for a 43–56% of responders, defined as patients off PPIs. A subset of patients in three of the studies[52, 54, 55] also underwent pre- and post-treatment pH monitoring; results showed no significant change in the study by Cipolletta *et al.*[52], whereas the series of the Vanderbilt University was split between responders and non-responders and showed a significant decrease in the former but not in the latter group.[53] A *post hoc* analysis of the U.S. open label trial has also been published,[62] which divided patients between responders and non-responders on the basis of post-treatment response for GERD health related QOL, heartburn, satisfaction and PPI use, and showed a decrease in oesophageal acid exposure in the responders only and a correlation between post-treatment heartburn score and oesophageal acid exposure.

These data suggest that symptomatic improvement after Stretta is attributable to a decrease in acid reflux and not, or at least not only, to desensitization of the oesophagus, as it was previously suggested.

Three abstracts have looked at long-term results of Stretta in 320 patients. Two of them showed a sustained effect on PPI use and GERD symptoms at 2–4 years,[59, 61] whereas one showed loss of effect of the procedure at 5 years.[60]

Table 2. Studies of sewing devices in patients with gastro-oesophageal reflux disease

First author (Ref.)	Year	Patients (*n*)	Device	Follow-up (months)	Patients off PPI (%)	pH < 4, pre/post (%)
Cadière[48]	2006	17	OesophyX	6	80	NA
Rothstein[51]	2006	78	Plicator	3	50	6.1/4.1 active group
		80			25	6.1/6.1 sham group
Schwartz[46]	2006	18	Endocinch	12	29	10/8 active group*
		20		3		10/8 sham group*
		20		3		
Schiefke[28]	2005	70	Endocinch	18	6	9.1/8.5 (at 12 months)

PPI, proton pump inhibitor; NA, not available.
* Values not given by the author but estimated from Figure 5 of their article.

Table 3. Studies of radiofrequency therapy in patients with gastro-oesophageal reflux disease

First author (Ref.)	Year	Patients (*n*)	Follow-up months (mean)	Patients off PPI (%)	% pH < 4 pre/post-procedure
Torquati[55]	2004	41 (follow-up 36)	18–34 (27)	56	6/3 (responders, $P < 0.01$) 8/10 (non-responders)
Go[53]	2004	50	3–32 (10)	29	NA
Cipolletta[52]	2005	32	12–26 (NA)	56	12/8
Lutfi[54]	2005	77 (follow-up 61)	6–36 (26)	43	8/5 (responders, $P < 0.01$) 9/7 (non-responders)
Haringsma[58]	2004	12	6	NA	10/6
Noar[59]	2005	227	6–48 (NA)	NA	NA
Arts[57]	2005	7	3	NA	18/13
Arts[56]	2006	11 (Sham)	3	NA	9/8
		11 (Stretta)	3	NA	16/17
Ryan[61]	2006	13	56–63 (NA)	31	11/7
Reymunde[60]	2006	80	48	86	NA

PPI, proton pump inhibitor; NA, not available.

Three more abstracts have looked into mechanisms of action of Stretta. One confirmed a significant decrease in the rate of tLESRs,[58] whereas the other two have shown a decrease in distensibility of the oesophago-gastric junction with the use of a barostat bag, which was not observed after the sham procedure, and have suggested that this may contribute to symptom control by decreasing refluxate volume.[56, 57]

Finally, the four full papers[52–55] and the abstract by Noar[59] have reported on the occurrence of complications. They observed either no or minor short-lasting complications, apart from two cases of gastroparesis[52, 54] one of which was transient and the other one lasted 4 months.

DISCUSSION

Despite the considerable number of published papers on, and the large number of patients treated with, endoscopic antireflux devices, the state of the art on these techniques is disappointing, to the degree that a plea for a moratorium in their clinical use has been proposed.[14] In fact, all the aspects of endoscopic therapy, except maybe for its safety, are either insufficiently explored or not investigated at all, or assessed in a particularly selected population of patients only. As an example of the last issue, most of the existing trials have included PPI-dependent patients with small to absent hiatal hernia and little evidence of oesophageal inflammation; there is no information regarding their potential use in patients with atypical GERD manifestations, and very little concerning special patient groups, such as the paediatric population.

We provide, in the Appendix, a list of recommendations for future reports of newly proposed devices/procedures for endoscopic treatment of GERD. Overall, clinical efficacy of endoscopic therapy seems not to be proven: many studies have shown a significant symptomatic improvement short term, as well as an improvement on QOL and a decrease in oesophageal acid exposure, but not the normalization of the latter. This, in turn, reflects a lack of persisting effect, and in fact no single technology has demonstrated long-term efficacy,[63, 64] leaving unsolved the issue of durability beyond 1–2 years. Furthermore, most devices have not been compared as yet with a sham procedure, and therefore their relative efficacy is simply not demonstrated. Moayyedi *et al.*,[1] for example, undertook a systematic review of randomized trial that assessed endoscopic therapy and was able to find only five trials that compared therapy with a sham procedure, for a total of 254 patients. They concluded that the number of treated patients is too small to allow any conclusion to be drawn.

Safety is probably the weakest feature of these techniques: Enteryx treatment, initially considered very safe, has been withdrawn from clinical practice by the manufacturer, despite its use in over 2600 patients; the same has occurred with Gatekeeper procedure and with Wilson ESD suturing device, whereas the Stretta

procedure, which is still available, has already been associated with at lest five deaths worldwide and a significant morbidity.

There are very few studies addressing the issue of cost, but it has been shown that, at least as far as the Enteryx, EndoCinch and Stretta procedures are concerned, their use would be cost-effective only if price decreases by at least 30%.[63] Interestingly, even if the FDA has approved some endoscopic procedure already in 2001 for clinical use, none of these devices has ever been granted with the Level I CPT code, the code level with the greatest likelihood of payer coverage in the USA.[65]

In conclusion, up to now, none of the proposed antireflux therapies has fulfilled the criteria of efficacy, safety, cost, durability and, possibly, of reversibility. This is witnessed by the overall lack of sham-controlled studies, by the spontaneous withdrawal from the market of the Enterix procedure or the non-availability of other two (the Wilson-Cook's ESD and the Medtronic's Gatekeeper), and by the lack of long-term studies. Conceivably, some effective endoscopic intervention might be available in the future, but no definite indication for endoscopic therapy of GERD is currently available.[64] Thus, we conclude that the EARPs proposed during the period 2000–2007 can be considered on the whole as a first, unsuccessful, round.

ACKNOWLEDGEMENT

Declaration of personal and funding interests: None.

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APPENDIX: A LIST OF SUGGESTIONS FOR AN IDEAL TRIAL ON ENDOSCOPIC GASTRO-OESOPHAGEAL REFLUX DISEASE THERAPY

From the experience we gathered by reviewing all the literature on this subject, we will suggest a list of critical issues to be examined within the setting of randomized-controlled trial before a new procedure is to be entered into clinical routine.

The first item is who will undergo the study, i.e. which patient should be included. We strongly believe that the present practice to restrict the indication to patients with mild oesophagitis and small or absent hiatal hernia limits the generalizability of results. Consequently, patients with all degrees of oesophagitis and hiatal hernia should be admitted.

Second, the individual physiological data should be assessed before and after the procedure in all individuals by means of state-of-the-art technology: we strongly suggest that state-of-the-art technology, such as oesophageal manometry and pH-impedance, need to be assessed pre-operatively and post-operatively.

Third, the outcome parameters should include a complete symptom assessment by means of a validated questionnaire, the endoscopic appraisal, a quality of life (QoL) score, and the antireflux drug consumption in this rank of hierarchy. Economical measures or QoL alone should not be considered as valid surrogate outcome measures.

In addition, the investigational procedure should be compared with as sham one; non-randomized studies cannot solve any clinically important questions, do inflate the number of poor quality studies, and create a logistic basis for too early dissemination of the technique.

Also, even short-term studies should incorporate an initial follow-up of at least 6 months. Some procedures may not remain in place following a short interval after the procedure, and therefore an early assessment may overestimate the true clinical results of it. Additionally, we believe that in our era of easy access and high quality information technology, a video recording of each individual procedure should be collected and maintained for a definite period, and should possibly be submitted (at least on request) together with the manuscript to the Journal where the study is intended to be published.

Finally, in no case should the marketing of a new procedure precede its comprehensive and sound scientific evaluation.