NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of endoscopic injection of bulking agents for gastro-oesophageal reflux disease

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared by NICE in August 2003.

Procedure name

- Endoscopic injectable treatment of a biopolymer.
- Endoscopic implantation treatment of a biopolymer.

Specialty societies

Specialist advice was sought from:

- *Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland.*
- *Association of Endoscopic Surgeons of Great Britain and Ireland.*
- *British Society of Gastroenterology.*

Description

Indications

Gastro-oesophageal reflux disease (GORD) is a common condition that can have a significant impact on the quality of life of an individual. It is caused by failure of the sphincter mechanism at the lower end of the oesophagus. Several factors alone or in combination can lead to the development of GORD such as impaired oesophageal clearance, hiatal hernia and delayed gastric emptying.

Symptoms of GORD can be broadly grouped into those directly related to reflux episodes such as heartburn, regurgitation and waterbrush, and those symptoms caused by complications of reflux disease including respiratory symptoms, dysphagia and painful swallowing (odynophagia).

Current treatment and alternatives

GORD may be managed through a combination of lifestyle modifications, antacid-antireflux drugs, prokinetic drugs and/or acid-suppressant agents or surgery.

Mild symptomatic GORD can usually be managed by the former options, whereas for patients with more severe symptoms or oesophagitis, intensive pharmacologic therapy or anti-reflux surgery may be needed. For most patients pharmacological therapy will be the mainstay of treatment.

What the procedure involves:

The procedure is carried out on an outpatient basis. The patient is sedated and given an injection of antibiotics. A needle catheter is then introduced through an endoscope into the gastro-oesophageal junction. This catheter is filled with a biocompatible polymer and solvent and is used to inject or implant the polymer into the gastro-oesophageal junction.

On completion of the injection, the needle is left in place for 30-60 seconds to allow complete polymerisation and avoid backflow of the solution.

Multiple injection/implants (around four) are performed in a circumferential manner around the oesophagus under fluoroscopic and endoscopic observation.

The procedure is stopped if a grey or black bulge is seen endoscopically in the submucosa, indicating that the polymer needs to be injected deeper and in a different site.

The aim of the procedure is to help keep stomach acid from backing up into the lower oesophagus by strengthening the muscle that separates the lower oesophagus from the stomach.

Efficacy:

Evidence of efficacy was based primarily on one uncontrolled study of 85 patients with GORD receiving chronic PPI therapy. This study reported that, at 12 months, 67% (57/85) of patients were no longer taking PPIs and that a further 9% (8/85) of patients had reduced PPI usage by 50% or more. Both heartburn and regurgitation symptom scores had improved at 12 months. Small reductions in acid reflux as assessed by measuring oesophageal PH were seen, but no improvement in endoscopic grades was observed. Efficacy of treatment was related to the residual implant volume, and repeat treatments may be required to enhance this volume.

The Specialist Advisors considered that this was a procedure in its infancy; and, as such, concerns about the efficacy of this procedure were unknown.

Safety:

Transient mild to moderate chest pain was the most commonly reported adverse event occurring after implantation; the incidence in the studies ranging between 53% (8/15) and 91.8% (78/85). Other complications included dysphagia, fever and nausea.

The Specialist Advisors had no major safety concerns..

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to endoscopic injectable treatment for gastro-oesphageal reflux disease (Appendix B). Searches were conducted via the following databases, covering the period from their commencement to June 2003: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Emphasis was placed on identifying good quality comparative studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, technical or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with gastroesophageal reflux disease.
Intervention/test	Endoscopic injection of a biopolymer.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

Studies included in the overview

This overview is based on three studies.

The largest study is an uncontrolled multicentre study.[1,2] Two papers have been published recently on this study. Both are presented below because the earlier paper provides more detailed safety information.[2]

The remaining two studies are small, uncontrolled case-series reports.

A list of abstracts presented on this procedure is provided in Appendix A of this document.

Table 1 Summary of key efficacy and safety findings from case series studies

Study details	Key efficacy findings	Key safety findings	Comments
Johnson et al (2003) [1] Non-controlled study 85 patients 6 sites US 1 site Belgium 1 site Canada Patients with well-controlled symptoms under PPI therapy. Mean age: 49.6 years (range 26.8–73.7 years) Follow up: 12 months	**Proton pump inhibitors (PPI) Responders** (intent to treat) 1 month: 83/85, 97.6% (95% CI = 88.4%–98.7%) 12 months (evaluable): 65/85, 76.5% (80.3%) (95% CI = 66.0%–85.0%) Patients able to discontinue PPIs completely at 12 months 67.1% (95% CI = 56.0%–76.9%). No evidence that reduction in PPI usage after procedure was shifting to other medications. **GERD HRQL heartburn** 65.9% (95% CI = 54.8%–75.2%) patients achieved a heartburn score ≤ 15 at 12 months ($p < 0.001$) **GERD HRQL regurgitation** 83.5% (95% CI = 73.9%–90.7%) patients achieved a regurgitation score ≤ 11 at 12 months ($p < 0.001$) **Quality of life physical** score improved from baseline $p < 0.001$ (no raw data) **Quality of life mental** score improved from baseline $p < 0.16$ (no raw data) PH and Manometry: Baseline / 12 months **Mean duration of monitoring**: 20.5 ± 3.5 hours / 19.5± 3.5 hours **Mean total number of pH<4 episodes**: 162.04 ± 112.12 / 114.82 ± 77.21, p=0.002 **Maximum duration of pH<4 episodes**: 33.50 ± 45.89 minutes / 21.40 ± 25.554 minutes, p=0.21 **Oesophagitis** (68 patients) At 12 months oesophagitis remained unchanged in 55.9% of patients, improved in 17.6% and worse in 26.5%. **Reimplantation**: 19 patients (22%) underwent reimplantation at 1 and 3 months	**Complications** All device- and procedure-related adverse events occurred during the initial 6 months follow up (detail provided in the earlier study)[2]	Clear inclusion and exclusion criteria 120 patients evaluated for inclusion, 85 enrolled, 8 patients elected to withdraw from study during follow up (6–12 months). No mention of how many patients recruited from each centre. Patients were classified as responders if they reduced PPI dosage by ≥ 50% No patient was treated under general anaesthesia. GERD-HRQL heartburn – validated measure 9 questions – using a Likert scale of 6 (0–5), summary score ranges 0–45. GERD-HRQL regurgitation – unvalidated questions. 4 questions – using a similar measure.

Study details	Key efficacy findings				Key safety findings	Comments
Johnson et al (2003) [2] Non-controlled study US 85 patients Patients with a BMI ≥ 35, hiatus hernia > 3 cm, grade 3 or 4 oesophagitis, or oesophageal motility disorder were excluded.	**GERD Symptom Score**	**Baseline**		**6 months**	**Complications** All classified as mild or moderate. **Device-related** ▪ 78 patients transient chest pain (91.8%) ▪ 17 patients dysphagia (20.0%) (all resolved within 12 weeks) ▪ 10 patients transient fever (11.8%) ▪ 6 patients burping (7.1%) ▪ 5 patients bloating (5.9%) ▪ 6 patients other (7.1%) **Procedure-related** ▪ 9 patients sore throat (10.6%) ▪ 7 patients vomiting (8.2%) ▪ 5 patients nausea (5.9%) ▪ 8 patients other (9.5%)	Clear inclusion and exclusion criteria Earlier study. GERD-HRQL heartburn – summary score ranges 0 (best)–45 (worst). GERD-HRQL regurgitation – summary score ranges from 0 (best)–20 (worst) SF-36: physical and mental components. Scores ranges from 0–100 with higher scores indicating improved functioning. Inconsistencies in the table 5 and text in the article.
		On PPIs	Off PPIs			
	GERD HRQL heartburn (81)	6.0 (2–9)	24.0 (22–31)	4.0 (0–11)		
	GERD HRQL regurgitation (81)	2.0 (0–4)	11.0 (8–14)	1.0 (0–5)		
	Significant difference between when patients were off PPIs at baseline and symptoms at 6 months $p < 0.001$					
	Quality of Life					
	SF-36 MCS (79)	54.0 (46–58)	52.7 (45–57)	55.9 (50–59)		
	SF-36 PCS (79)	51.0 (41–56)	44.8 (35–52)	50.8 (43–57)		
	Significant difference between when patients were off PPIs at baseline and symptoms at 6 months $p < 0.001$					
	Medication use	**3 months**		**6 months**		
	Off all PPIs	69/85 (81.2%)		60/81 (74.1%)		
	Dose reduced > 50%	8/85 (9.4%)		8/81 (9.9%)		
	Dose reduced < 50%	0/85 (0%)		1/81 (1.2%)		
	Dose maintained	7/85 (8.2%)		11/81 (13.6)		
	Dose increased	1/85 (1.2%)		1/81 (1.2%)		
	PH-metry and Manometry	**Baseline (off PPIs)**		**6 months**		
	pH ≤ 4 (%) total (71)	9.50 (7–16)		7.00 (3–11) $p < 0.001$		
	pH ≤ 4 (%) upright (60)	10.3 (7–15)		8.9 (4–13) $p = 0.015$		
	pH ≤ 4 (%) supine (60)	6.50 (1–17)		1.85 (0–5) $p = 0.026$		
	Longest episode (69)	17.0 (9–30)		13.0 (6–24) $p = 0.100$		
	LES pressure (74)	12.45 (9–19)		12.05 (9–19) $p = 0.657$		
	LES length (61)	2.0 (2–3)		3.0 (2–4) $p = 0.004$		
	Reimplantation/retreatment: 19 patients underwent repeat treatment. At 6 months 12/19 had symptoms scores demonstrating benefit.					

Study details	Key efficacy findings			Key safety findings	Comments
Deviere et al (2003) [3-6] Non-controlled study Brussels and Rome June 1999 and June 2000 Patients had an established diagnosis of GORD including oesphagitis. 15 patients Age range: 36–72 years Follow up: 4–12 months (median 6 months)		**Baseline**	**4–12 months**	**Complications** ▪ 8 patients transient pain ▪ 1 patient mild dysphasia	Authors note that when a ring was observed during injection, follow-up radiograph examinations always revealed persistence of the ring. Limited information. Authors note that this was a pilot study.
	Heartburn (1 asymptomatic to 4 severe heartburn)	9 patients grade 3 5 patients grade 4 3.40 ± 0.13 (mean)	6 patients grade 1 7 patients grade 2 2 patients grade 4 1.87 ± 0.26 (mean)		
	LES pressure mmHg	12.2 ± 0.9	16.7 ± 1.3		
	LES pressure, increased in 10 patients, same in two patients, decreased in 3 patients at 4–12 months **PPIs** 4 patients had to resume medication 2 patients most of the implanted material was lost by 6-month follow up				
Peters et al (2003) 7 Non-controlled study US 9 patients (34 implants) Patients had underlying oesophageal disease severe enough to warrant oesophagectomy. Follow up: unclear	30/34 (88%) implants were successfully placed into the wall of the oesophagus The remaining four were found lying subserosally or attached to the exterior of the GEJ			**Complications** Authors report 'no untoward reactions'	Small study. Limited/no information on patient characteristics. Limited outcomes.

Abbreviations:
GERD HRQL: Gastro-oesophageal reflux disease health related quality of life
LES: lower esophageal pressure

Validity and generalisability of the studies

- There is currently limited evidence available on this procedure. The first peer-reviewed published paper on this procedure appeared in 2003.
- The study of 85 patients is the most rigorous and helpful of the studies included in this overview.[1,2]
- In general, the outcomes of this study have been measured well by the authors.[1,2]
- The authors also provide both an intent to treat analysis (taking into account the eight withdrawals) and an analysis of evaluable patients. It is worth noting, however, that pH and Monometry measurements were only available for 69 patients.
- In terms of quality of reporting, some of the figures in the paper do not include raw data. There would also appear to be some inconsistencies in the presentation of results between the earlier and the later paper. [2,1]
- As in most studies on endoscopic outpatient procedures, selection of patients has largely been restricted to those with reflux and a small or no hiatal hernia, no dysphasia or structure, absence of Barrett's mucosa and good symptom control with acid suppressing medications.

Specialist advisors' opinions

Specialist Advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

- Procedure in its infancy.
- Potential to be beneficial because of the large number of patients with reflux.
- Awaiting longer-term results.

Issues for consideration by IPAC

- It was noted in a review paper on this technique that two multicentre studies are currently been conducted in the United States, Canada and Europe.[8] One of these studies being the report by Johnston et al.[1,2]
- There are a significant number of abstracts on this procedure. It is likely, given the involvement of the manufacturer in this procedure, that further peer-reviewed published data will become available in the near future.

References

1 Johnson DA, Ganz R, Aisenberg J, Cohen LB, et al. Endoscopic implantation of enteryx for treatment of GERD: 12-month results of a prospective multicenter trial. *American Journal of Gastroenterology* 2003; 98(9):1921–30.

2 Johnson DA, Ganz R, Aisenberg J, Cohen LB, et al. Endoscopic, deep mural implantation of Enteryx for the treatment of GERD: 6-month follow-up of a multicenter trial. [comment]. *American Journal of Gastroenterology* 2003; 98(2): 250–8.

3 Deviere J, Pastorelli A, Louis H, de M V, et al. Endoscopic implantation of a biopolymer in the lower esophageal sphincter for gastroesophageal reflux: a pilot study. *Gastrointestinal Endoscopy* 2002; 55(3):335–41.

4 Deviere J, Louis H. Endoscopic implantation of a biopolymer in the lower esophageal sphincter for gastroesophageal reflux. *Endoscopy* 2002; 34(10):849.

5 Deviere J, Louis H. Endoscopic implantation of a biopolymer in the lower esophageal sphincter for gastroesophageal reflux. *Acta Endoscopica* 2002; 32(3):247–8.

6 Costamagna G, Riccioni ME, Mutignani M, Perri V, et al. Endoscopic treatment of gastroesophageal reflux: Implantation of a biopolymer (enteryx) in the lower oesophageal sphincter. *Giornale Italiano di Endoscopia Digestiva* 2002; 25(3):215–20.

7 Peters JH, Silverman DE, Stein A. Lower esophageal sphincter injection of a biocompatible polymer: accuracy of implantation assessed by esophagectomy. *Surgical Endoscopy* 2003; 17(4):547–50.

8 Louis H, Deviere J. Endoscopic implantation of Enteryx for the treatment of gastroesophageal reflux disease: Technique, pre-clinical and clinical experience. *Gastrointestinal Endoscopy Clinics of North America* 2003; 13(1):191–200.

Appendix A: Relevant abstracts on the procedure

Study details	Patients/ follow up	Comments
Johnson DA, Aisenberg J, Cohen LB, Deviere J, et al. Enteryx, an injectable treatment for GERD: multicenter results. *American Journal of Gastroenterology* 2002; 97(9 Suppl). S12	170	Same authors as studies 2 and 18.
Johnson DA, Aisenberg J, Cohen L, Deviere J, et al. Enteryx(TM) solution, a minimally invasive injectable treatment for GERD: initial multicenter human trial results. *The American Journal of Gastroenterology* 2001; 96(1):S17–S18.	-	Initial results.
Ganz RA. Community experience with enteryx(R), a minimally invasive therapy for the treatment of GERD. *The American Journal of Gastroenterology* 2003; 98(1):S6.	24 (14 evaluable)	Subgroup analysis on the one of the sites providing patients in studies 2 and 18.

A number of other abstracts are also listed on website of the company involved in this procedure. This includes an additional nine abstracts presented on this procedure during the 2003 digestive disease week; the most significant are listed below.

Study details	Patients/ follow up	Comments
Louis H., Van Gansbeke D., Silverman D., Deviere J. Three year follow-up for initial GERD patients injected with EVOH polymer. DDW Poster Presentation, May 19 2003	8 patients 3 year follow up	Abstract
Ganz R, Aisenbert J, Cohen L. Enteryx solution, a minimally invasive injectable treatment for GERD: analysis of endoscopy findings at 12 months. DDW Poster Presentation, May 19 2003	68 patients 12 months follow up	Abstract
Lehman G.A, Hieston K.J, Aisenberg J, Cohen L, et al. Enteryx solution, a minimally invasive injectable treatment for GERD: current worldwide multicenter human trial results	176 patients 12 months follow up	Abstract

Appendix B: Literature search for endoscopic injectable treatment for gastro-oesophageal reflux disease.

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PredMedline and all EMB databases.

For all other databases a simple search strategy using the key words in the title was employed.

#	Search history
1	enteryx.mp.
2	polymer.ti.
3	*POLYVINYLS/
4	biopolymers.ti.
5	exp Absorbable Implants/
6	or/2-5
7	gastroesophageal reflux.mp. or exp Gastroesophageal Reflux/
8	GORD.tw.
9	GERD.tw.
10	or/7-9
11	10 and 6
12	1 or 11