NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease is caused by backward movement (reflux) of the stomach contents into the oesophagus. This occurs when the ring of muscles at the lower end of the oesophagus fails to work properly. This procedure involves implanting material into these muscles with the aim of bulking the sides of the oesophagus to stop the reflux.

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 December 2006.

Procedure name

Endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of gastro-oesophageal reflux disease

Specialty societies

Specialist advice was sought from:

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

Description

Indications

Gastro-oesophageal reflux disease (GORD) is a common condition. It is caused by failure of the sphincter mechanism at the lower end of the oesophagus. Several factors alone or in combination can also predispose the development of GORD such as impaired oesophageal clearance, hiatus hernia and delayed gastric emptying.

Symptoms of GORD are those directly related to reflux episodes, such as heartburn and retrosternal chest pain, regurgitation, waterbrash and those symptoms caused by complications of reflux disease which may include respiratory symptoms, dysphagia and painful swallowing (odynophagia). In some individuals GORD may be a predisposing factor for the development of metaplastic changes (Barrett's oesophagus) or the development of oesophageal stricture.

Current treatment and alternatives

Mild symptomatic GORD can be managed through a combination of lifestyle modifications, antacid-antireflux drugs, pro-kinetic drugs and acid-suppressant agents. For most patients pharmacological therapy will be the mainstay of treatment. Patients with who are refractory to pharmacological therapy may require anti-reflux surgery.

Assessment of treatment efficacy includes improvement in the GORD Heartburn-Related Quality of Life (GORD/GERD-HRQL) scale, improvements in Short-Form Health Survey (SF-36), normalisations of oesophageal pH-metry and manometry scores and a reduction in the need for antireflux medication.

What the procedure involves

The procedure is usually carried out under sedation on an outpatient basis. An endoscope is introduced through an overtube into the gastro-oesophageal junction. A vacuum is then created and a fold of the inner layers of the oesophagus is aspirated into the shelf of the overtube under fluoroscopic and endoscopic observation. A delivery sheath is then inserted into the oesophageal submucosa in the overtube and a hydrogel prosthesis is implanted. Multiple implants are then injected in a circumferential manner around the oesophageal wall. The prostheses then fully expand creating folds in the oesophageal wall.

This procedure can be repeated. The implants can also be removed if necessary.

Efficacy

The Specialist Advisers listed the key efficacy outcomes as reduction in symptoms, quality of life, medication usage and normalisation of oesophageal manometry and pHmetry.

The evidence on efficacy is based on two case series [1, 2] totalling 78 patients, each with 6 months follow-up.

Symptoms and quality of life

In one case study (n = 69) GORD/heartburn-related quality of life (GORD-HRQL) was significantly improved at 6 months (score of 5; n = 64) compared with baseline (score of 24; n = 53) ($p < 0.05$). Regurgitation scores were also significantly improved compared with baseline measurements (16 [n = 55] versus 2 [n = 49]; $p < 0.05$) [1]. Significant improvement in quality of life at 6 months compared with baseline was reported in respect to the physical measures (score 43 versus 52; $p < 0.05$) but not the mental component as measured by the SF-36. (score 49 versus 50; not significant) [1].

Similar results were reported in a case series of 9 patients, with median GORD/heartburn-related quality of life improving from 35.5 at baseline to 9.4 at 6 months follow-up ($p<0.01$). No quality of life data was reported.

Oesophagitis
Oesophagitis was reported in one study. In this study oesophagisits was present at baseline in 58% of patients (39/67) and in 32% (17/53) at 6 months.

PH-metry (acid exposure)
In the case series of 9 patients, acid exposure time of the distal oesophagus decreased, but only reached normal levels in 3 of the patients. In the case series of 69 patients, of whom data was available for 45 patients; only 18 patients (40%) had a normal pH level at 6 months.

The Specialist Advisers expressed uncertainty as to durability of the efficacy of procedure. They also commented that few patients have a sustained reduction in objective measures such as oesophageal acid exposure following implantation.

Safety

One study reported safety data. In this case series the most common complication reported was erosion of the prosthesis (15/67; 22%) (no further details reported) [1]. One patient also suffered a pharyngeal perforation during overtube insertion.

The Specialist Advisers listed potential complications as pharyngeal perforation, mucosal erosions and migration of device.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to endoscopic injectable treatment for GORD (appendix B). Searches were conducted via the following databases, covering the period from their commencement to 11th December 2006: 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 gastro-oesophageal reflux disease
Intervention/test	Endoscopic implantation of a hydrogel prostheses
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 two case series studies.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (Table 2) has been listed in appendix A.

Existing reviews on this procedure

Three health technology reviews/summaries were identified that assessed this procedure.

1. Medical Services Advisory Committee: Horizon Scanning Technology Summary. Gatekeeper reflux repair system. Literature search date: September 2004.

2. Canadian Coordinating Office for Health Technology Assessment (CCOHTA). Endoscopic-based Treatments for Gastro-oesophageal Reflux . Publication date: March 2004

3. Blue Cross Blue Shield. Transesophageal endoscopic treatments for gastroesophageal reflux disease. Technology evaluation centre. Literature search date: September 2002.

The current overview includes all of the procedure related literature that has been cited in the above three reviews.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in each piece of guidance listed below.

Interventional procedures

Related indication

Endoscopic injection of bulking agents for gastro-oesophageal reflux disease. *NICE Interventional procedures guidance no. 55 (2004). Available from:* **www.nice.org.uk/IPG055**

Endoluminal gastroplication for gastro-oesophageal reflux disease. *NICE Interventional procedures guidance* no. 115 (2004). Available from: **www.nice.org.uk/IPG115**

Technology appraisals

None relevant

Clinical guidelines

Dyspepsia: Managing dyspepsia in adults in primary care. *NICE clinical guidelines no 17 (2004) Available from* **http://www.nice.org.uk/guidance/CG17.** This guidance does not specifically relate to this procedure.

Public health

None relevant

Table 2 Summary of key efficacy and safety findings for endoscopic injection of bulking agent for GORD

Abbreviations used: BMI, body mass index; GORD/GERD, gastro-(o)esophageal reflux disease; GERD-HRQL, Heartburn-related Quality of Life score; ITT, intent to treat; MCS, mental component summary; NS, not stated; PPI, proton pump inhibitors; PCS, physical component summary;SF-36, Short-form Health Survey , LOS – lower oesophageal sphincter

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Fockens et al (2004) [1]

Case series

Several centres: Holland, Italy, Norway, Germany, UK, France, Switzerland

Study period: not stated

n = 69 (67 treated with 77 procedures)

Population: Mean age 47.2 years (range 19–70), including 49 men (73%) and 18 women (27%); mean BMI 26.3 (range 18.1–34.9). 3 patients had short-segment Barrett’s oesophagus 2 cm or less. Oesophagitis was present in 38 patients (grade 1: 18 patients; grade 2: 20 patients). Hiatal hernias up to 3 cm were present in 42/65 patients.

Indications: GORD symptoms of heartburn and regurgitation in patients who responded well to PPI therapy. Patients had to have abnormal 24-hour pH-metry while not receiving PPI therapy, with PH < 4 for 4% of the total time.

Technique: Submucosal placement of the gatekeeper prostheses.</td>
<td>Implantation (endoscopically assessed)

In the 77 procedures, 270/290 prostheses were inserted successfully (93%). In 20 delivery attempts, the prosthesis was either mis-positioned at the time of insertion or extruded partially from the mucosa after insertion; 9/20 mis-positioned prostheses were removed endoscopically at the time of the initial procedure.

At 6 months (n = 54; no data on 12 patients)

• 19/54 (35%) had all prostheses

• 12/54 (22%) had at least 75–100% of prostheses

• 16/54 (30%) had at least 50–75%

• 6/54 (11%) had less than 50% of their prostheses

• 1/54 (2%) had none.

Repeat procedure
10 patients (14.5%) received a re-do procedure, within an average of 6 weeks after the initial operation.</td>
<td>Authors note that the incidence of serious adverse events within 30 days of the initial procedure was 3.0%, with 2 patients being admitted to hospital (one with perforation requiring and one with unexplained nausea requiring removal of the implant).

The perforation occurred as it was not possible to introduce the overtube into the oesophagus. The patient was hospitalised for 1 week, surgical intervention was not required.

Cumulative adverse events (n = 34) within 6 months of the procedure in 67 patients (note that that the totals don’t reconcile to the table given in the text).

<table>
<tr><th>Adverse events</th><th>1 mth</th><th>3mths</th><th>6mths</th></tr>
<tr><td>Erosion of prosthesis</td><td>3</td><td>10</td><td>15</td></tr>
<tr><td>Nausea and vomiting and weight loss</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Retrosternal pain</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Tiredness and poor sleep</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Stomach pain</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Skin rash</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Cough</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>Erosive duodenitis</td><td>0</td><td>2</td><td>2</td></tr>
<tr><td>Positive Helicobacter pylori</td><td>1</td><td>1</td><td>1</td></tr>
</table>
</td>
<td>For this study data from two European multicentre trials were pooled.

Patients were enrolled consecutively.

One patient withdrew before treatment.

Seven patients withdrew from the study early: one declined treatment, one withdrew because of nausea and vomiting, and one because of a pharyngeal perforation; three declined further participation after the implantation (no reason given) and in one patient the implant proved to be defective and the patient declined to have another procedure.

The initial primary efficacy outcome was an improvement in GERD-HRQL score.

Two weeks after the procedure patients were asked to discontinue PPI therapy. If a patient had persistent GORD symptoms 4–6 weeks after the initial procedure and was not on medication the surgeon could choose whether to implant</td>
</tr>
</table>

Abbreviations used: BMI, body mass index; GORD/GERD, gastro-(o)esophageal reflux disease; GERD-HRQL, Heartburn-related Quality of Life score; ITT, intent to treat; MCS, mental component summary; NS, not stated; PPI, proton pump inhibitors; PCS, physical component summary;SF-36, Short-form Health Survey , LOS – lower oesophageal sphincter

Study details

Patients resumed PPI medication for 2 weeks after the procedure.

Follow-up: 6 months

Conflict of Interest: Not stated

Key efficacy findings

Clinical efficacy

All scores showed significant improvement from baseline.

Time point	GERD-HRQL	Regurgitation
Baseline on PPIs	13.0 (7.0–21.5) n = 64	100 (6–15) n = 55
Baseline off PPIs	24 (16–30) n = 64	16 (10–22) n = 55
1 month off PPIs	8 (2–14 n = 61 p < 0.05	3 (0–7) n = 55 p < 0.05
3 months off PPIs	4 (1.0-11.5) n = 56 p < 0.05	1 (0–6) n = 49 p < 0.05
6 months off PPIs	5 (1–15) n = 53 p < 0.05	2 (0–8) n = 49 p < 0.05

Quality of life

Time point	SF-36 PCS	SF-36 MCS
Baseline on PPIs	48.8 (42.6–52.3) n = 64	50.4 (42.4–55.5) n = 64
Baseline off PPIs	43.3 (36.4–49.0) n = 60	49.0 (36.4–56.1) n = 60
1 month off PPIs	51.4 (46.1–55.4) n = 61 p < 0.05	50.4 (44.4–56.2) n = 61 p = NS
3 months off PPIs	53.7 (45.7–56.5) n = 57 p < 0.05	53.3 (47.1–57.2) n = 57 p = NS
6 months off PPIs	52.4 (46.6–56.0) n = 57 p < 0.05	49.7 (46.1–55.1) n = 57 p = NS

Key safety findings

rapid test			
Clostridium difficile enterocolitis induced	0	1	1
Pharyngeal tear during overtube insertion	1	1	1
Hoarseness	0	1	1
Defective device	1	1	1
Diverticular disease	0	0	1
Worsening of depression	0	1	1
Multiple small ulcerations on prostheses	0	0	1
Scheduled for out-of-protocol visit	0	1	1
Not specified	0	1	1
Total	12	26	34

Comments

additional prostheses.

Data are not available on all patients for all outcomes measured.

Numbers in the text do not always reconcile.

Authors note that a number of patients refused to undergo repeat endoscopy.

Authors note that the mechanical mechanism of action for the clinical efficacy of this procedure is not known.

Abbreviations used: BMI, body mass index; GORD/GERD, gastro-(o)esophageal reflux disease; GERD-HRQL, Heartburn-related Quality of Life score; ITT, intent to treat; MCS, mental component summary; NS, not stated; PPI, proton pump inhibitors; PCS, physical component summary;SF-36, Short-form Health Survey , LOS – lower oesophageal sphincter

Study details	Key efficacy findings	Key safety findings	Comments
	Medication use Authors note that data on medication use for all patients in each of the centres were not collected systematically, and at some centres data on medication use were not recorded. **Endoscopy (reflux oesophagitis)** Baseline – 38/69 patients (55%) At 6 months – 17/53 patients (32%) **pH-metry** Number of individual upright and supine episodes were also significantly reduced compared with baseline.		

	Total time proportion pH < 4	Total reflux episodes
Baseline n = 66	9.1 (6.0–14.3)	95.5 (55.0–157.0)
6 months n = 45	6.1 (2.9–10.2) p < 0.05	52.0 (27.0–96.0) P < 0.05

	Manometry (mmHg)
Baseline (n = 65)	8.8 (6.0–13.8)
6 months (n = 42)	13.8 (9.3–19.5) p < 0.005

Abbreviations used: BMI, body mass index; GORD/GERD, gastro-(o)esophageal reflux disease; GERD-HRQL, Heartburn-related Quality of Life score; ITT, intent to treat; MCS, mental component summary; NS, not stated; PPI, proton pump inhibitors; PCS, physical component summary;SF-36, Short-form Health Survey , LOS – lower oesophageal sphincter

Study details	Key efficacy findings	Key safety findings	Comments
Cicala M, Gabbrielli A, Emerenziani S et al. (2005) [2] **Case series** Italy Study period: not stated **n = 9** Population: Mean age 48 years including 4 men and 3 women). Indications: GORD symptoms of heartburn and regurgitation in patients who responded well to PPI therapy. Patients had to have abnormal 24-hour pH-metry, with PH < 4 for 4% of the total time. Technique: Submucosal placement of the gatekeeper prostheses. **Follow-up: 6 months** Conflict of Interest: not stated	**GORD HRQL** Improved from a mean baseline value of 35.5 to a mean value of 9.4 at six months follow-up ($p<0.01$). All patients except one showed significant improvement in the symptom score after six months of follow-up. Manometrc data No significant differences were found for resting and residual LOS pressure (12.1 vs 15.3 p=NS), LOS length (2.4 versus 2.7 p=NS) pHmetric data Acid exposure time at the distal oesophagus decreased from 11.7% at baseline to 7.7% at follow-up. Of the nine patients, distal acid exposure time normalised in three. Acid exposure time at the middle and proximal oesophagus decreased significantly in all patients. Proximal extent of acid events significantly decreased in all patients at follow-up (37% vs 9.5%).	The authors do not report on complications.	Limited demographic details were reported. Dynamic characteristics of GORD in patients were also compared with those in 13 asymptomatic controls.

Validity and generalisability of the studies

- The published evidence base for this procedure is limited to two publications reporting on fewer than a hundred patients who were followed-up for up to 6 months.
- Safety data were only reported by one study.
- In one study [1] it was noted that outcome data were not available for medication usage as it had not been collected systematically by the centres involved in the study.
- While subjective symptoms seem to improve there does not seem to be a corresponding improvement in objective measurements such as manometry.
- The longest follow-up is 6 months which does not allow assessment of the durability of the procedure.
- 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 (i.e those with less severe GORD).

Specialist advisers' opinions

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

Professor Bailey, Mr Barr, Mr Dehn, Dr Ireland, Dr Trudgill.

- Uncertain safety and efficacy.
- No studies demonstrating long term efficacy.
- Short term trials report symptom improvement and some reduction in proton pump inhibitor usage but much less commonly any change in acid exposure on oesophageal pH monitoring
- This is one of a number of endoscopic methods which could be used to reduce PPI dependence in reflux patients.
- A number of endoscopic methods of treating GORD have been withdrawn from the market because of lack of efficacy or untoward side effects/complications.
- Few centres are undertaking this procedure.
- Unlikely to become established as a clinical therapy at present without extensive modification to the procedure and appropriate clinical trials

Issues for consideration by IPAC

- None of the Specialist Advisers have performed this procedure.
- From other review papers [3] it would appear that other studies have been undertaken on this procedure however their results have not been published.
- It is worth nothing that a procedure using an overall similar concept but a different bulking agent and injection technique has now been voluntarily withdrawn from the market following the death of the patient from extramural administration of the agent.
- It is difficult to ascertain the true rate of serious adverse events with the examined procedure, due to the limited data.

References

1. Fockens P, Bruno MJ, Gabbrielli A et al. (2004) Endoscopic augmentation of the lower esophageal sphincter for the treatment of gastroesophageal reflux disease: Multicenter study of the Gatekeeper Reflux Repair System. Endoscopy.Vol.36(8)()(pp 682-689), 2004. 682-689.

2. Cicala M, Gabbrielli A, Emerenziani S et al. (2005) Effect of endoscopic augmentation of the lower oesophageal sphincter (Gatekeeper reflux repair system) on intraoesophageal dynamic characteristics of acid reflux. Gut.Vol.54(2)()(pp 183-186), 2005. 183-186.

3. Johnson DA. (2005) Enteryx implant for gastroesophageal reflux disease. Current Treatment Options in Gastroenterology.Vol.8(1)()(pp 51-57), 2005. 51-57.

Appendix A: Additional papers on endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of gastro-oesophageal reflux disease not included in summary table 2

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Study details	Patients/ follow up	Comments
Fockens P. (2003) Gatekeeper reflux repair system: Technique, pre-clinical, and clinical experience. *Gastrointestinal Endoscopy Clinics of North America* .13(1):179–189.	Case series (prosthetic hydrogel)	Preclinical and clinical results. Overlap with [1]

Appendix B: Related NICE guidance for endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of gastro-oesophageal reflux disease

Guidance programme	Recommendation
Interventional procedures	**IPG055 Endoscopic injection of bulking agents for gastro-oesophageal reflux disease (under review)** 1.1 Current evidence on the safety and efficacy of endoscopic injection of bulking agents for gastro-oesophageal reflux disease does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to undertake endoscopic injection of bulking agents for gastro oesophageal reflux disease should take the following action. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. Use of the Institute's *Information for the Public* is recommended. • Audit and review clinical outcomes of all patients having endoscopic injection of bulking agents for gastro-oesophageal reflux disease. 1.3 Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. The Institute may review the procedure upon publication of further evidence.
	IPG115 Endoluminal gastroplication for gastro-oesophageal reflux disease. 1.1Current evidence suggests that there are no major safety concerns associated with endoluminal gastroplication for gastro oesophageal reflux disease (GORD). However, evidence of efficacy is not adequate for this procedure to be used without special arrangements for consent and for audit or research. 1.2 Clinicians wishing to undertake endoluminal gastroplication for GORD should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's efficacy and provide them with clear written information. Use of the Institute's Information for the public is recommended.

Guidance programme	Recommendation
	• Audit and review clinical outcomes of all patients having endoluminal gastroplication for GORD. 1.3 Publication of efficacy outcomes will be useful in reducing the current uncertainty. The Institute may review the procedure upon publication of further evidence.
Technology appraisals	None relevant
Clinical guidelines	None relevant
Public health	None relevant

Appendix C: Literature search for endoscopic augmentation of the lower oesophageal sphincter using hydrogel implants for the treatment of gastro-oesophageal reflux disease

Databases	Version searched (if applicable)	Date searched
The Cochrane Library	The Cochrane Library 2005, Issue 3	2/09/2005
CRD		5/09/2005
Embase	1980 to 2005 Week 35	2/09/2005
Medline	1966 to August Week 4 2005	2/09/2005
PreMedline	September 01, 2005	2/09/2005
CINAHL	1982 to August Week 4 2005	2/09/2005
British Library Inside Conferences (limited to current year only)		5/09/2005
National Research Register	2005 Issue 3	2/09/2005
Controlled Trials Registry		5/09/2005

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in other databases.

Search strategy used in Medline

1. gastroesophageal reflux/
2. gord.tw.
3. gerd.tw.
4. (gastro-oesophageal adj3 reflux).tw.
5. (gastroesophageal adj3 reflux).tw.
6. (gastro-esophageal adj3 reflux).tw.
7. (gastrooesophageal adj3 reflux).tw.
8. or/1-7
9. polyvinyls/
10. injections, intralesional/
11. (bulking adj3 agent$).tw.
12. enteryx.tw.
13. absorbable implants/
14. polymers/
15. biopolymers/
16. (bio$ adj2 (polymer$ or copolymer$)).tw.
17. (polymer$1 or biopolymer$1).tw.
18. biocompatible materials/
19. gatekeeper$.tw.
20. or/9-19
21. 8 and 20
22. animal/ not human/
23. 21 not 22