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Transoral Incisionless Fundoplication for Refractory Gastroesophageal Reflux Disease: Where Do We Stand?

Deepanshu Jain[1] and Shashideep Singhal[2]

[1]Department of Internal Medicine, Albert Einstein Medical Center, Philadelphia, PA, [2]Division of Gastroenterology, Hepatology and Nutrition, University of Texas Health Science Center at Houston, Houston, TX, USA

Gastroesophageal reflux disease (GERD) is a chronic, progressive, and costly medical condition affecting a substantial proportion of the world population, predominantly the Western population. The available treatment options for patients with refractory GERD symptoms are limited to either laparoscopic surgery with significant sequelae or potentially lifelong, high-dose proton pump inhibitor therapy. The restoration of the antireflux competence of the gastroesophageal junction at the anatomic and physiologic levels is critical for the effective long-term treatment of GERD. Transoral incisionless fundoplication (TIF) surgery is a safe, well-tolerated, and effective treatment that has yielded significant symptomatic improvement in patients with medically refractory GERD symptoms. In this review article, we have summarized case series and reports describing the role of TIF for patients with gastroesophageal reflux symptoms. The reported indications, techniques, complications, and success rates are also discussed. **Clin Endosc 2016;49:147-156**

Key Words: Endoscopic fundoplication; Gastroesophageal reflux; Proton pump inhibitors

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a chronic, progressive, and costly medical condition affecting a substantial proportion of the world population, predominantly the Western population. The first clinical description of GERD appeared in 1935 as a case report on severe peptic esophagitis.[1] GERD symptoms interrupt the activities of daily living and have been associated with significantly increased work absenteeism, reduced productivity at work,[2-6] and increased healthcare resource utilization.[6]

During the previous years, many medical and surgical treatment options have been devised; however, they all are expensive and pose significant adverse effects, which paved the way for the invention and advancement of effective endoscopic treatment options. Transoral incisionless fundoplication (TIF) is a unique form of natural orifice surgery, representing a next step in the field of minimally invasive surgery for the treatment of GERD.

TIF is an endoscopic luminal procedure that restores the antireflux competence of the gastroesophageal junction (GEJ), a critical step for effective long-term treatment of GERD. TIF is based on the principles of conventional antireflux surgery. It is done by using the EsophyX device (EndoGastric Solutions, Redmond, WA, USA), which is inserted transorally under endoscopic visual guidance to reconstruct the gastroesophageal valve (GEV) by wrapping the proximal part of the stomach (fundus) around the distal end of the esophagus, thus reestablishing the reflux barrier. The procedure involves placement of fasteners at four different positions to create a ≥270° valve that is 1 to 3 cm in length. Owing to this endoscopic incisionless approach, patients undergoing TIF experience less discomfort and faster recovery than those undergoing traditional antireflux surgery. Clinical studies have shown that TIF is an effective and safe treatment for mild to moderate GERD

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Correspondence: Shashideep Singhal
Division of Gastroenterology, Hepatology and Nutrition, University of Texas Health Science Center at Houston, 6431 Fannin, MSB 4.234, Houston, TX 77030, USA
Tel: +1-347-446-8203, **Fax:** +1-713-500-2107, **E-mail:** sdsinghal@gmail.com

symptoms in carefully selected patients.[7] The major and minor adverse events experienced with TIF compares favorably with those reported for laparoscopic fundoplication.[7] TIF has helped patients in stopping acid-suppressive therapy, by maintaining or inducing the remission of GERD symptoms.[8]

In this review article, we have summarized case series and reports describing the use of TIF for GERD patients. The indications, techniques, clinical response, endoscopic response, limitations, and complications reported are also discussed.

MATERIALS AND METHODS

An extensive English-language literature search was done by using PubMed, Medline, and Google to identify peer-reviewed original and review articles by using the key terms "endoscopic fundoplication" and "GERD." Only articles on human patients were selected. The references of pertinent studies were manually searched to identify additional relevant studies. The indication, procedural details, technical and clinical success rates, complications, and limitations were considered part of the inclusion criteria. The search yielded mostly retrospective and prospective studies with a modest sample size, including case reports, case series, and randomized controlled trials.

None of the authors have any conflicts of interest or financial relationship with the company that produces or distributes the device described in the review article.

RESULTS

Ten original articles were considered appropriate for inclusion in this review. Among them, seven were prospective studies from the United States of America,[8-10] Belgium,[11] Netherlands,[12,13] and Italy.[14] Others included a retrospective study,[15] a case report,[16] and a prospective sham controlled trial[17] from the United States. All cases are summarized in Table 1.

Indications

Initially, TIF was approved by the Food and Drug Administration only for chronic GERD patients who are responsive to proton pump inhibitors (PPIs); however, over time, the inclusion criteria for TIF have expanded. Currently, the most common indication for TIF is either patients with refractory chronic GERD symptoms with only partial response to acid-suppressive medications,[8-10,12-15,17] or those who do not want to continue lifelong medications despite being responsive to acid-suppressive medications.[11,13,15] Kumta et al.[16] described a unique case of TIF used for gastroesophageal reflux symptoms that developed after an endoscopic myotomy for underlying achalasia.

Exclusion criteria

The experience with TIF has grown in last few years but only to a specific segment of GERD patients. In nine of 10 studies included in our review, patients with a body mass index of >35 kg/m^2, hiatal hernia >2 cm, grade D esophagitis according to the Los Angeles classification, esophageal motility disorder, and Barrett's esophagus were excluded from the study.[8-15] A history of failed antireflux surgery was also one of the exclusion criteria in a few studies.[11-13]

Technique

The EsophyX device has been designed by Endogastric Solutions for the treatment of GERD. The use of the EsophyX2 device with a flexible endoscope has been the method of choice for most physicians performing TIF.

The procedure is performed under general anesthesia and requires the assistance of two physicians (surgeons and/or gastroenterologists). The first physician controls the EsophyX device; thus, monitoring the appropriate application of fasteners to secure the newly created GEV, and the second physician ensures continuous direct visualization with the endoscope. The device creates a GEV by retracting full-thickness plications and through the tailored placement of multiple fasteners circumferentially around the GEJ.[18]

There have been different versions of the TIF protocol with the major difference being in the degree of circumference of the reestablished valve, i.e., 220° in the 1.0 protocol versus 240° in the 2.0 protocol, and the location of the valve, i.e., at the level of the GEJ in the 1.0 protocol in contrast to the 2.0 protocol where the valve is created at a distance of 3 to 5 cm from the GEJ (Fig. 1).[19] Cadière et al.[11] described the use of the TIF 1.0 protocol in his study of 86 patients undergoing TIF with a mean wrap of 230° (160° to 300°), whereas the TIF 2.0 protocol was used in most of the other studies[8,10,13-15,17] with a minimum reported wrap of 240°[10,15] to as high as 300°.[15] In addition, the length of the reconstructed valve has been reported to vary from as low as 2 cm[10,11,15] to as high as 6 cm.[11]

Clinical response

The authors have used a wide variety of objective scales to quantify the GERD symptoms before and after TIF, such as the GERD health-related quality of life (GERD-HRQL),[8,10-15] GERD symptom score (GERSS),[10,15] reflux symptom index (RSI),[8,10,15] reflux disease questionnaire (RDQ),[8,17] and GERD quality of life (GERD-QUAL).[14] Each of these scores, GERD-HRQL,[20] GERSS,[21] RSI,[22] RDQ,[23] and GERD-QUAL,[24] have been validated for assessing the GERD symptom severity and the response to the treatment.

Table 1. Comparative Description of Different Studies Evaluating the Role of Transoral Incisionless Fundoplication

Study/ country	Type of study	Intervention	Indication	Exclusion criteria	Total subjects/subjects lost to follow-up	Instrument	Technique/ extent of wrap around the esophagus/ length of reconstructed valve	Clinical response	Endoscopic response	PPI requirement	Follow-up period	Peri-procedure complications (requiring extended hospital stay)	TIF failure requiring second endoscopic/surgical intervention	Other complications (persistent >1 mo, post TIF)	Miscellaneous facts
Trad et al. (2014)[8] USA	Prospective, randomized, multicenter, crossover study	TIF	1. Daily regurgitation or atypical symptoms (Montreal criteria) on PPI 2. Abnormal 48 hr ambulatory pH test 3. H/O daily PPI use for at least 6 mo	1. BMI >35 2. Barrett's esophagus >2 cm 3. Hill grade valve III or IV 4. Hiatal hernia >2 cm in either dimension 5. Los Angeles grade C or D classification	40/1	EsophyX-2 device via flexible endoscope	TIF 2.0 protocol	1. Resolution of regurgitation and atypical symptoms 1) 6 mo: 13/20 (65%) 2) 12 mo: 30/39 (77%) 2. Mean GERD-HRQL 1) Baseline: 26.25 2) 6 mo: 5.23 3) 12 mo: 5.41 3. Mean RDQ 1) Baseline: 2.91 2) 6 mo: 0.35 3) 12 mo: 0.50 4. Mean RSI 1) Baseline: 22.00 2) 6 mo: 4.64 3) 12 mo: 4.79	1. Healed esophagitis 1) 6 mo: 18/20 (90%) 2) 12 mo: 19/19 (100%) 2. Normalized esophageal pH 1) 6 mo: 21/39 (54%) 2) 12 mo: 17/38 (45%) 3. Mean Demeester score (48 hr pH study) 1) Baseline: 35.28 2) 6 mo: 23.64 3) 12 mo: 25.32	1. Baseline 1) Daily: 100% 2) Occasional: 0% 3) None: 0% 2. 6 mo 1) Daily: 2% 2) Occasionally: 8% 3) None: 90% 3. 12 mo 1) Daily: 3% 2) Occasionally: 15% 3) None: 82%	12 mo	None	None	Flatulence: 1/39	-
		High dose PPI for first 6 mo, followed by TIF			23/2	Maximal labelled dose of PPI, split into twice daily regimen for 6 mo followed by EsophyX-2 device via flexible endoscope	TIF 2.0 protocol	1. Resolution of regurgitation and atypical symptoms 1) 6 mo: 1/21 (0.05%) 2) 12 mo: 6/9 (67%) 2. Mean GERD-HRQL 1) Baseline: 26.43 2) 6 mo: 18.86 3) 12 mo: 10.05 3. Mean RDQ 1) Baseline: 3.04 2) 6 mo: 2.14 3) 12 mo: 1.33 4. Mean RSI 1) Baseline: 22.62 2) 6 mo: 19.62 3) 12 mo: 8.76	1. Healed esophagitis 1) 6 mo: 5/13 (38%) 2) 12 mo: 11/13 (85%) 2. Normalized esophageal pH 1) 6 mo: 11/21 (52%) 2) 12 mo: 7/21 (33%) 3. Mean Demeester score (48 hr pH study) 1) Baseline: 35.79 2) 6 mo: 19.29 3) 12 mo: 28.60	1. Baseline 1) Daily: 100% 2) Occasionally: 0% 3) None: 0% 2. 6 mo 1) Daily: 100% 2) Occasionally: 0% 3) None: 0% 3. 12 mo 1) Daily: 10% 2) Occasionally: 9% 3) None: 71%		None	None	None	
Toomey et al. (2014)[9] USA	Case-control study with prospective follow-up	TIF	GERD refractory to or requiring open ended medical therapy	1. Hiatal hernia >2 cm 2. Esophageal dysmotility	20	EsophyX-2 device via flexible endoscope	DNA	1. Patient satisfaction at follow-up: 67% 2. Patients with symptom frequency (<1/mo): 83%	DNA	DNA	DNA	None	None	None	OT: 71 min HSL: 1 day
		Toupet fundoplication	GERD refractory to or requiring open ended medical therapy with abnormal esophageal motility	1. Failed surgical fundoplication in past	20	DNA	LESS	1. Patient satisfaction at follow-up: 92% 2. Patients with symptom frequency (<1/mo): 92%	DNA	DNA	DNA	DNA	NA	DNA	OT: 85 min HSL: 1 day 10%: operation related complication (severity not reported)

Table 1. Continued

Study/ country	Type of study	Intervention	Indication	Exclusion criteria	Total subjects/subjects lost to follow-up	Instrument	Technique/ extent of wrap around the esophagus/ length of reconstructed valve	Clinical response	Endoscopic response	PPI requirement	Follow-up period	Peri-procedure complications (requiring extended hospital stay)	TIF failure requiring second endoscopic/surgical intervention	Other complications (persistent >1 mo, post TIF)	Miscellaneous facts
		Nissen fundoplication	GERD refractory to or requiring open ended medical therapy with normal esophageal motility	1. Failed surgical fundoplication in past 2. Esophageal dysmotility	20	DNA	LESS	1. Patient satisfaction at follow-up: 86% 2. Patients with symptom frequency (<1/mo): 80%	DNA	DNA	DNA	DNA	NA	DNA	OT: 119 min HSL: 2 day 5%: procedure related complication (severity not reported)
Wilson et al. (2014)[10] USA	Prospective multicenter trial	TIF	Chronic GERD (>1 yr), daily PPI use >6 mo, with unsatisfactory response	1. Hiatal hernia >2 cm (axial), >3 cm (transverse) 2. BMI >35 3. Esophageal achalasia 4. Barretts esophagus >2 cm 5. Reflux esophagitis-grade D Los Angeles classification 6. Miscellaneous: gastroparesis, Zenker diverticulum, gastroparesis, scleroderma	100/4	EsophyX-2 device via flexible endoscope	TIF 2.0 protocol 240–330 2–5 cm	1. Median GERD-HRQL 1) Baseline: 24 2) 6 mo: 4 3) 12 mo: 2 2. Median GERSS 1) Baseline: 26 2) 6 mo: 4 3) 12 mo: 4 3. Median RSI 1) Baseline: 20 2) 6 mo: 5 3) 12 mo: 4	1. Esophagitis 1) Healed (12 mo): 13/17 (76%) 2) Improved (12 mo): 2/17 (12%) 2. Esophageal acid exposure 1) Normalization (12 mo): 14/27 (52%)	1. Baseline 1) Daily: 92% 2) Occasionally: 8% 3) None: 0% 2. 6 mo 1) Daily: 11% 2) Occasionall: 9% 3) None: 80% 3. 12 mo 1) Daily: 23% 2) Occasionally: 3% 3) None: 74%	12 mo	None	1. 5/96: underwent LNF (1 had severe vomiting post procedure, 2 were non compliant with dietary instructions, other 2-unspecified reason) 2. 1/96: underwent repeat TIF	At 12 mo 1) *De novo* dysphagia: 2 2) *De novo* bloating: 1 3) Worsening flatulence: 2	-
Cadière et al. (2008)[11]	Prospective multicenter	TIF	18–80 yr, chronic GERD (>6 mo) responsive to PPI therapy, with symptom recurrence on discontinuation of PPI for 14 day	1. Irreducible hiatal hernia >2 cm 2. Previous failed anti-reflux surgery 3. BMI ≥35 4. Delayed gastric emptying 5. Esophageal disease-motility disorder, ulcer, biopsy proven Barretts, stricture 6. Reflux esophagitis-grade D Los Angeles classification	86/7	EsophyX-2 device via flexible endoscope	TIF 1.0 protocol 230 (160–300) 4 cm (2–6)	Median GERD-HRQL 1) Baseline: 24 2) 6 mo: 5 3) 12 mo: 7	Median Demeester score 1) Baseline: 34 2) 6 mo: 24 3) 12 mo: 28	1. Baseline 1) Daily: 100% 2) Occasional: 0% 3) None: 0% 2. 6 mo 1) Daily: 14/86 (17%) 2) Occasionally: 14% 3) None: 69% 3. 12 mo 1) Daily: 12/86 (15%) 2) Occasionally: 16% 3) None: 68%	12 mo	1. Esophageal perforation 2/86: successfully repaired surgically 2. Post TIF intraluminal bleeding-treated with endoscopic clips, fibrin glue, and blood transfusion	3/86 LNF (2 were post perforation during TIF, and the third one-reason not specified)	1. Abdominal pain: 1/86 2. Nausea: 1/86	-
Rinsma et al. (2015)[12] Netherlands	Prospective, randomized, controlled, multicenter trial	Continuation of PPI therapy	Chronic GERD (>6 mo), partially responsive to acid suppressive medication	1. Hiatal hernia > 2 cm 2. Previous failed anti-reflux surgery 3. BMI ≥35 4. Esophageal motility disorder on manometry 5. Barretts esophagus 6. Reflux esophagitis-grade D Los Angeles classification	15	NA	NA	Mean GERD-HRQL 1) Baseline: 26.0 2) 6 mo: 23.6	1. Distal baseline impedance (Ω) 1) Baseline: 1,088 2) 6 mo: 2,470 2. Acid exposure time (%) 1) Baseline: 12.4 2) 6 mo: 5.9 3. Mean acid reflux episodes 1) Baseline: 65.6 2) 6 mo: 33.9	NA	6 mo	NA	NA	NA	-

Table 1. Continued

Study/ country	Type of study	Intervention	Indication	Exclusion criteria	Total subjects/subjects lost to follow-up	Instrument	Technique/ extent of wrap around the esophagus/ length of reconstructed valve	Clinical response	Endoscopic response	PPI requirement	Follow-up period	Peri-procedure complications (requiring extended hospital stay)	TIF failure requiring second endoscopic/surgical intervention	Other complications (persistent >1 mo, post TIF)	Miscellaneous facts
		TIF			32	EsophyX-2 device via flexible endoscope	DNA	Mean GERD-HRQL 1) Baseline: 23.7 2) 6 mo: 8.5	1. Distal baseline impedance (Ω) 1) Baseline: 1,769 2) 6 mo: 2,294 2. Acid exposure time (%) 1) Baseline: 9.7 2) 6 mo: 6.9 3. Mean acid reflux episodes 1) Baseline: 63.2 2) 6 mo: 39.3	DNA	6 mo	DNA	None	DNA	
Rinsma et al. (2014)[13] Netherlands	Prospective single center study	TIF	Chronic GERD (>6 mo), on PPI therapy, dissatisfied or unwilling to continue lifelong PPI therapy	1. Hiatal hernia >2 cm in length 2. Previous failed anti-reflux surgery 3. Esophageal stricture or ulcer 4. Esophageal motility disorder on manometry 5. Barretts esophagus 6. Reflux esophagitis-grade D Los Angeles classification 7. Current pregnancy 8. Severe comorbidity- cardiopulmonary disorder, coagulation disorder, portal hypertension, immunosuppression, morbid obesity	15	EsophyX-TM device via flexible endoscope	TIF 2.0 protocol	Mean GERD-HRQL 1) Baseline: 27.5 2) 6 mo: 13.2	1. Mean EGJ distensibility (mm^2/mm of Hg) 1) Baseline: 2.4 2) 6 mo: 1.6 2. 24-hr ambulatory impedance pH (upright acid exposure time) (%) 1) Baseline: 11.7 2) 6 mo: 6.6 3. 24-hr ambulatory impedance pH (liquid reflux episodes) (%) 1) Baseline: 30.4 2) 6 mo: 16.7 4. Total no. of TLESR 1) Baseline: 16.8 2) 6 mo: 9.2	1. Baseline 1) Daily: 100% 2) None: 0% 2. 6 mo 1) Daily (same dose): 1/15 (6.7%) 2) Daily (decreased dose): 3/15 (20%) 3) None: 11/15 (73.3%), but 1 used non PPI antisecretory medication	6 mo	DNA	None	DNA	-
Testoni et al. (2015)[14] Italy	Prospective single center study	TIF	Symptomatic GERD, on PPI (standard dose twice a day) for a minimum of 3 mo	1. Hiatal hernia >3 cm 2. Previous esophageal, gastric or major abdominal surgery 3. Atypical GERD symptoms 4. Biopsy prove Barretts esophagus 5. Esophageal stricture 6. Severe comorbidity-cardiopulmonary disease and collagen disease	50	EsophyX-TM device via flexible endoscope	TIF 2.0 protocol	1. Mean GERD-HRLQ 1) Baseline (on PPI): 20 2) Baseline (off PPI): 46 3) 12 mo: 16 4) 24 mo: 17 2. Mean GERD-QUAL 1) Baseline (on PPI): 84 2) Baseline (off PPI): 114 3) 12 mo: 71 4) 24 mo: 80	1. pH metry, Johnson Demeester score 1) Baseline: 22 2) 6 mo: 18 3) 24 mo: 19 2. Impedance, total refluxes (number) 1) Baseline: 66 2) 6 mo: 38 3) 24 mo: 43 3. LES pressure (mm Hg) 1) Baseline: 8 2) 6 mo: 11 3) 24 mo: 12	1. 6 mo 1) Stopped PPI: 61.2% 2) Halved PPI: 22.5% 3) On PPI: 16.3% 2. 12 mo 1) Stopped PPI: 51.0% 2) Halved PPI: 28.6% 3) On PPI: 20.4% 3. 6 yr 1) Stopped PPI: 35.7% 2) Halved PPI: 50.0% 3) On PPI: 14.3%	6 yr	Pneumothorax: 2 subjects- treated successfully with immediate transthoracic drainage	4/50 LNF at 12 mo secondary to persistent GERD symptoms	DNA	-

Table 1. Continued

Study/ country	Type of study	Intervention	Indication	Exclusion criteria	Total subjects/subjects lost to follow-up	Instrument	Technique/ extent of wrap around the esophagus/ length of reconstructed valve	Clinical response	Endoscopic response	PPI requirement	Follow-up period	Peri-procedure complications (requiring extended hospital stay)	TIF failure requiring second endoscopic/surgical intervention	Other complications (persistent >1 mo, post TIF)	Miscellaneous facts
Trad et al. (2012)[15] USA	Retrospective	TIF	1. Persistent GERD and/LPR symptoms, not/partial controlled on antisecreatory medications 2. Either dissatisfied with current therapy or unwilling to continue taking medications indefinitely	1. Hiatal hernia, axial dimension >2 cm	34/6	EsophyX-2 device via flexible endoscope	TIF 2.0 protocol 270 (240–300) 3 cm (2–4)	1. Median GERD-HRQL 1) Baseline: 26 2) 14 mo: 4 2. Median GRESS score 1) Baseline: 24 2) 14 mo: 3 3. Median RSI 1) Baseline: 17 2) 14 mo: 4	24-hr pH (only 2 subjects) 1. First subject: Demeester score 1) Baseline: 29 2) Post-TIF at 14 mo: 24.5 2. Second subject 1) Baseline: abnormal pH 2) Post-TIF at 14 mo: normal pH	1. Baseline 1) Daily: 25/28 (89%) 2) Occasional: 3/28 (11%) 3) None: 0/28 2. 14 mo 1) Daily: 5/28 (18%) 2) Occasionally: 5/28 (18%) 3) None: 18/28 (64%)	14 mo	None	1/28 LNF (likely cause failure of dietary restriction post-TIF, causing disruption of reconstructed valve)	None	-
Kumta et al. (2015)[16] USA	Case report	TIF	Subject with achalasia, who underwent peroral endoscopic myotomy and developed reflux symptoms refractory to PPI	None	1	DNA	270	DNA	DNA	DNA	DNA	DNA	DNA	DNA	-
Hunter et al. (2015)[17] USA Prospective sham controlled mutlicenter study		TIF f/b 6 mo of placebo treatment	18–80 yr age group with chronic GERD (>6 mo) symptoms and troublesome regurgitation despite daily PPI (40 mg) use	1. Systemic disease: not well controlled 2. BMI >35 3. Esophageal ulcer or stricture 4. Current pregnancy or plan of pregnancy in next 12 mo 5. Hiatal hernia >2 cm 6. Barrett's esophagus >2 cm 7. Esophagitis: Grade C or D Los Angeles classification 8. Esophageal dysmotility 9. Previous esophageal or gastric surgery 10. Peptic ulcer disease 11. Gastric outlet obstruction or gastroparesis 12. Portal hypertension or coagulopathy 13. Immunosuppression	81/1	EsophyX-2 device via flexible endoscope	TIF 2.0 protocol 270 (200–340) 3 cm (mid-portion); 1 cm (either corner)	1. Elimination of troublesome regurgitation (6 mo): 54/81 (67%) 2. Median regurgitation RDQ score 1) Baseline (on PPI): 3.5 (3–4.3) 2) 6 mo (on placebo): 0.5 (0–1.5) 3. Median Heartburn RDQ score 1) Baseline (on PPI): 2.6 (1.5–3.8) 2) 6 mo (on placebo): 0.5 (0–1.6) 4. Composite median heartburn and regurgitation RDQ score 1) Baseline (on PPI): 3.1 (2.4–3.8) 2) 6 mo (on placebo): 0.6 (0–1.3)	1. Total no. of reflux episodes 1) Baseline: 135 2) 6 mo: 94 2. Percent time pH <4 1) Baseline: 9.3 2) 6 mo: 6.4 3. DeMeester Score 1) Baseline: 33.6 2) 6 mo: 23.9	By ITT analysis 1) 3 mo: 10/87 (11%) resumed PPI 2) 18 mo: 24/87 (28%) resumed PPI	6 mo	None	By ITT analysis 1. Treatment failure 1) 3 mo: 10/87 (11%), all resumed PPI, no other intervention done 2) 18 mo: 24/87 (28%), all resumed PPI, no other intervention done	None	-

Table 1. Continued

Study/ country	Type of study	Intervention	Indication	Exclusion criteria	Total subjects/subjects lost to follow-up	Instrument	Technique/ extent of wrap around the esophagus/ length of reconstructed valve	Clinical response	Endoscopic response	PPI requirement	Follow-up period	Peri-procedure complications (requiring extended hospital stay)	TIF failure requiring second endoscopic/surgical intervention	Other complications (persistent >1 mo, post TIF)	Miscellaneous facts
	Sham surgery f/b 6 mo of PPI therapy				38/1	EGD and 15 F maloney dilator	30 min for EGD and 15 min for Maloney dilator	1. Elimination of troublesome regurgitation (6 m): 17/38 (45%) 2. Median Regurgitation RDQ score 1) Baseline (on PPI): 3.8 (2.9–4.5) 2) 6 mo (on PPI): 0.8 (0–2) 3. Median Heartburn RDQ score 1) Baseline (on PPI): 3.0 (2.0–4.1) 2) 6 mo (on PPI): 0.8 (0–2) 4. Composite heartburn and regurgitation RDQ score 1) Baseline (on PPI): 3.3 (2.5–4.0) 2) 6 mo (on PPI): 0.9 (0.1–2.0)	1. Total no. of reflux episodes 1) Baseline: 125 2) 6 mo: 122 2. Percent time pH <4 1) Baseline: 8.6 2) 6 mo: 8.9 3. DeMeester score 1) Baseline: 30.9 2) 6 mo: 32.7	DNA	6 mo	None	By ITT analysis 1. Treatment failure 1) 3 mo: 15/42 (35.7%), 12/15 underwent crossover to TIF 2) 18 mo: 30/42 (71.4%) underwent crossover to TIF	NA	

PPI, proton pump inhibitor; TIF, transoral incisionless fundoplication; H/O, history of; BMI, body mass index; GERD-HRQL, gastroesophageal reflux disease-health-related quality of life; RDQ, reflux disease questionnaire; RSI, reflux symptom index; DNA, data not available; LESS, laparo-endoscopic single site; NA, not available; OT, operating time; HSL, hospital stay length; GERSS, GERD symptom score; LNF, laparoscopic Nissen fundoplication; EGJ, esophagogastric junction; TLESR, transient lower esophageal sphincter relaxation; LPR, laryngopharangeal reflux; f/b, followed by; ITT, intention-to-treat analysis.

Trad et al.[8] described a significant decrease in the mean GERD-HRQL (26.25 to 5.41), mean RDQ (2.91 to 0.50), and mean RSI scores (22.0 to 4.79) after TIF at 12 months follow-up. The study also showed that the TIF group (mean GERD-HRQL [26.25 to 5.23], mean RDQ [2.91 to 0.35], and mean RSI scores [22.0 to 4.64]) showed better outcomes than the high-dose PPI group (mean GERD-HRQL [26.43 to 18.86], mean RDQ [3.04 to 2.14], and mean RSI scores [22.62 to 19.62]) at 6 months follow-up.[8] The high-dose PPI group showed further decreases in mean GERD-HRQL (18.86 to 10.05), mean RDQ (2.14 to 1.33), and mean RSI scores (19.62 to 8.76) at 6 months after TIF.[8] Toomey et al.[9] described the patient satisfaction scores (67%, 92%, and 86%) and the proportions of patients with a frequency of symptoms of <1/month (83%, 92%, and 80%) at postintervention follow-up across three subgroups (TIF, Toupet fundoplication, and Nissen fundoplication). Wilson et al.[10] revealed a decrease in the median GERD-HRQL (24 to 2), median GERSS (26 to 4), and median RSI score (20 to 4) post-TIF at 12 months follow-up. Cadière et al.[11] showed a decrease in the median GERD-HRQL scores from 12 to 7 at 12 months post-TIF. Rinsma et al.[12] described a decrease in the mean GERD-HRQL score from 23.7 to 8.5 post-TIF in contrast to almost similar results in the mean GERD-HRQL scores (26.0 to 23.6) in the PPI study arm at 6 months follow-up. In another study, Rinsma et al.[13] showed a similar trend in the mean GERD-HRQL scores (27.5 to 13.2) post-TIF at 6 months follow-up. The study by Testoni et al.[14] did not show a significant difference in GERD-HRQL (from 20 to 17) and GERD-QUAL (84 to 80) post-TIF at 2 years follow-up. In another study by Trad et al.,[15] the results showed a decreasing trend in median GERD-HRQL (26.0 to 4), median RDQ (24 to 3), and median RSI scores (17 to 4) post-TIF at 14 months follow-up. Hunter et al.,[17] in a recent study, reported the elimination of troublesome regurgitation symptoms at 6 months follow-up in 54 of 81 patients (67%) who underwent TIF and placebo treatment, in contrast to 17 of 38 patients (45%) who underwent a sham procedure and PPI therapy. The trend in the median regurgitation RDQ score (3.5 to 0.5), median heartburn RDQ score (2.6 to 0.5), and composite median regurgitation and heartburn RDQ scores (3.1 to 0.6)

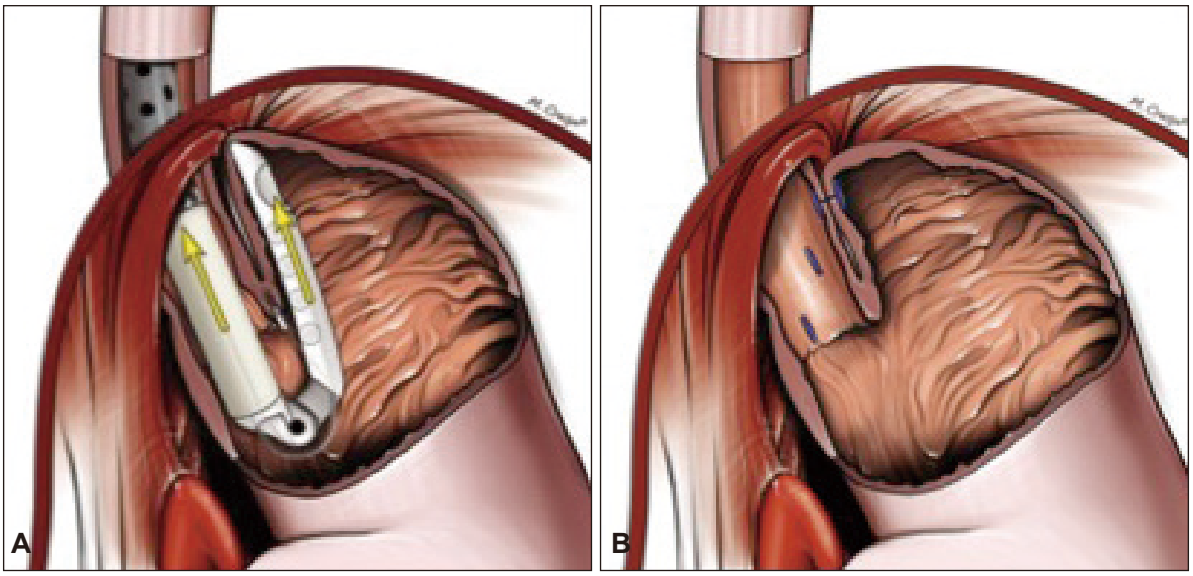

Fig. 1. (A) Creation of esophagogastric fundoplication using the EsophyX device (EndoGastric Solutions). (B) Post procedure appearance-esophagogastric fundoplication proximal to the Z-line. Adapted from Bell et al.[19]

among patients who underwent TIF and placebo medication was similar to that in patients who underwent a sham procedure and PPI treatment (median regurgitation RDQ score [3.8 to 0.8], median heartburn RDQ score [3.0 to 0.8], and composite median regurgitation and heartburn RDQ score [3.3 to 0.9]) at 6 months follow-up.[17]

Overall, the results of the above studies seem to be reflective of the improvement in the quality of life of GERD patients after TIF.

Endoscopic response

Trad et al.[8] described a significant decrease in the mean Demeester score (35.28 to 25.32) with normalization of esophageal pH in 45% (17 of 38) of patients, and healing of esophagitis in 100% of patients (19 of 19) post-TIF at 12 months follow-up. The study also showed that the TIF group (mean Demeester score [35.28 to 23.64] with normalization of esophageal pH in 54% of patients [21 of 39] and healed esophagitis in 90% of patients [18 of 20]) showed better outcomes than the high-dose PPI group (mean Demeester score [35.79 to 19.29] with normalization of esophageal pH in 52% of patients [11 of 21] and healed esophagitis in only 38% of patients [5 of 13]) at 6 months follow-up.[8] The high-dose PPI group showed further improvement in the proportion of patients with healed esophagitis (85%, 11 of 13) but a poor response reflected in the mean Demeester score (19.29 to 28.60) with normalization of esophageal pH in only 33% (7 of 21) of patients at 6 months after TIF.[8] Wilson et al.[10] reported normalization of esophageal acid exposure in 52% (14 of 27) of patients with healed esophagitis in 76% of patients post-TIF at 12 months follow-up. Cadière et al.[11] showed a decrease in the median Demeester score (34 to 28) post-TIF at 12 months follow-up. Rinsma et al.[12] described an improvement in distal baseline impedance (1,769 to 2,294 Ω) with a decrease in acid exposure time (9.7% to 6.9%) and mean acid reflux episodes (63.2 to 39.3) in the post-TIF group, which was comparable to those in the PPI group (improvement in distal baseline impedance [1,088 to 2,470 Ω]; decrease in acid exposure time [12.4% to 5.9%] and mean acid reflux episodes [65.6 to 33.9]) at 6 months follow-up. In another study, Rinsma et al.[13] showed an improvement in multiple endoscopically measured parameters, such as the mean GEJ distensibility (2.4 to 1.6 mm^2/mm Hg), upright acid exposure time (11.7% to 6.6%), liquid reflux episodes (30.4% to 16.7%), and mean number of transient lower esophageal sphincter relaxation episodes (16.8 to 9.2) post-TIF at 6 months follow-up. Testoni et al.[14] also reported a mild improvement in Demeester score (22 to 19) with a decrease in the total number of reflux episodes (66 to 43) and an increase in lower esophageal sphincter pressure (8 to 12 mm Hg) post-TIF at 2 years follow-up. Trad et al.[15] reported only two patients at 14 months follow-up, with one showing normalization of esophageal pH and the other showing a decrease in Demeester score from 29 to 24.5. Hunter et al.[17] reported a statistically significant (p<0.001) improvement in the Demeester score (33.6 to 23.9), percent time with pH <4 (9.3% to 6.4%), and number of reflux episodes (135 to 94) in patients who underwent TIF and placebo treatment in contrast to those who underwent a sham procedure and PPI therapy (Demeester score [30.9 to 32.7], percent time with pH <4 [8.6% to 8.9%], and number of reflux episodes [125 to 122])

at 6 months follow-up.

Overall, the results of the studies seem to be reflective of effective esophageal mucosal healing in most of the GERD patients after TIF, thus indirectly decreasing the risk of the complications of chronic GERD.

PPI requirement

The proportion of patients requiring PPIs to control their GERD symptoms is one of the indirect measures of efficacy of the underlying intervention for GERD.

Trad et al.[8] reported a significant decline in the proportion of daily PPI users (100% to 3%), with a concomitant increase in the proportion of occasional PPI users (0% to 15%) and those who do not use PPIs (0% to 82%) post-TIF at 12 months follow-up. The high-dose PPI group also showed a similar trend in the proportion of daily PPI users (100% to 10%) with a concomitant increase in the proportion of occasional PPI users (0% to 9%) and those who remain not using PPIs (0% to 71%) at 6 months after TIF.[8] Wilson et al.[10] reported a decline in the proportion of daily PPI users (92% to 23%) and occasional PPI users (8% to 3%) with concomitant increase in patients who remain not using PPIs (0% to 74%) after TIF at 12 months follow-up. Cadière et al.[11] also showed a decline in the proportion of daily PPI users (100% to 15%) with a concomitant increase in the proportion of occasional PPI users (0% to 16%) and those who remain not using PPIs (0% to 68%) after TIF at 12 months follow-up. Rinsma et al.[13] showed a similar trend, with 11 of 15 patients (73.3%) stopping their PPI use altogether and the remaining 4 of 15 users (26.7%) reporting daily use, but with 3 of the 4 daily users not able to decrease the daily dose of PPI, at 6 months after TIF. The study by Testoni et al.[14] was unique in comparison to the rest of the studies because of its long follow-up of 6 years. The results showed that after TIF, the proportion of daily PPI users decreased at 6 months (100% to 16.3%) and at 6 years (16.3% to 14.3%) follow-up. There was a concomitant increase in patients who were using half the PPI dose at 6 months (0% to 22.5%) and at 6 years (22.5% to 50.0%) follow-up.[14] In addition, the proportion of patients who have stopped PPI initially increased (0% to 61.2%) and then decreased (61.2% to 35.7%) at 6 years follow-up.[14] In another study, Trad et al.[15] reported a decreasing trend in the proportion of daily PPI users (89% to 18%) with a concomitant increase in the proportion of occasional PPI users (11% to 18%) and those who remain not using PPIs (0% to 64%) post-TIF at 14 months follow-up. Hunter et al.[17] reported that of 87 patients who underwent TIF with placebo treatment, 10 patients (11%) at 3 months follow-up and 24 patients (28%) at 18 months follow-up resumed PPI therapy because of the failure to resolve the GERD symptoms.

Overall, the results of the above studies are reflective of a significant decrease in the proportion of GERD patients requiring PPI after TIF, which indirectly has a major impact in decreasing the incidence of PPI-related complications among these patients.

Follow-up

Most authors reported a follow-up period ranging from a minimum of 6 months[12,13,17] to a maximum of 6 years.[14] A total of 575 patients were studied in the 10 studies included in our review, among whom 22 patients were lost to follow-up. Despite a good follow-up, many patients with a successful control of symptoms after fundoplication might still be compliant to clinical questionnaire surveys on return visits but are nearly universally noncompliant to follow-up pH monitoring, thus leaving fewer patients for a comparison of the endoscopic outcomes.

TIF failure

Of the 575 total patients, 492 underwent TIF, 14 (2.84%) of whom required a repeat intervention. One patient underwent a repeat TIF procedure[10] and the other 13 required laparoscopic fundoplication.[10,11,14,15] Of these 13 cases, four were secondary to persistent GERD symptoms,[14] two were secondary to esophageal perforation post-TIF,[11] three were secondary to noncompliance to post-TIF dietary recommendations,[10,15] one was secondary to severe post-TIF vomiting,[10] and the other three had unknown etiology.[10,11] Hunter et al.[17] reported TIF failure in 10 of 87 (11%) patients at 3 months and 24 of 87 (28%) patients at 18 months follow-up, necessitating the resumption of PPI use; however, none of the patients underwent a repeat TIF or laparoscopic surgery. In the same study, Hunter et al.[17] reported that among the group who underwent sham surgery with placebo medication, 15 of 42 patients (35.7%) at 3 months and 30 of 42 patients (71.4%) at 18 months follow-up underwent TIF for persistent GERD symptoms.

Periprocedural complications (requiring extended hospital stay)

Of the 575 total patients, 492 underwent TIF, five (1.01%) of whom required an extended hospital stay secondary to the procedure-related complication. Of these five patients, two had esophageal perforation that required surgical treatment;[11] two had pneumothorax that was treated with transthoracic drainage;[14] and the other one had gastrointestinal bleeding that was treated with endoscopic clips, fibrin glue, and supportive blood transfusion.[11]

Long-term procedure-related adverse effects (persistent/*de novo* >1 month post-TIF)

Of the 575 total patients, 492 underwent TIF, of whom

only eight (1.62%) were reported to have had symptoms that persisted beyond 1 month after TIF, or completely new symptoms that appeared 1 month after TIF that were attributed to the procedure. Three patients had worsening flatulence at 12 months follow-up,[8,10] two had *de novo* dysphagia at 12 months follow-up,[10] one had *de novo* bloating at 12 months follow-up,[10] one had persistent abdominal pain at 1 month follow-up,[11] and the other one had persistent nausea at 1 month follow-up.[11]

CONCLUSIONS

TIF for chronic GERD can be a safe, minimally invasive, and equally efficacious alternative approach to surgery in selected patients who have refractory symptoms or are reluctant to take lifelong acid-suppressive medications or have contraindications to surgery. With the evolving technique and increasing experience, TIF seems to be a reasonable first-line approach for the management of a specific subgroup of patients with chronic GERD. The preliminary reports appear promising; however, larger multicentric prospective randomized sham-controlled trials with a longer follow-up and head-to-head comparison between PPI and other modalities for the treatment of GERD are needed in the future to ascertain its benefits before it can be adopted as a standard alternative therapy for patients with chronic GERD.

Conflicts of Interest

The authors have no financial conflicts of interest.

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