Original Article

The role of transoral incisionless fundoplication (TIF) in the management of gastroesophageal reflux disease (GERD) following peroral endoscopic myotomy (POEM): A pilot, prospective, patient-driven study

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Abstract

Background: Gastroesophageal reflux (GERD) is a concern after peroral endoscopic myotomy (POEM). Transoral incisionless fundoplication (TIF) has been recently described as a possible therapy for post-POEM GERD in case series.

Methods: We prospectively enrolled patients undergoing POEM who agreed to participate in objective post-procedure GERD evaluation. Patients with objective evidence of GERD and suitable anatomy were offered TIF vs. proton pump inhibitor (PPI) only. Patients who underwent TIF were compared to those on PPI-only therapy after follow-up.

Results: Of 21 enrolled POEM patients with objective testing, GERD was found in 11 (52%). Of those eligible for TIF, 4 (40%) opted to pursue TIF and were compared to those on PPI-only therapy ($n = 6$). Three months post-TIF, 75% of patients had discontinued or significantly decreased PPI. There were no adverse events. GERD health-related quality of life scores were low and comparable between TIF (3.75 ± 6.2) and those who remained on PPI-only therapy (4.1 ± 5).

Conclusion: In this pilot, patient-driven prospective study, 75% of patients with post-POEM GERD undergoing TIF had stopped or significantly reduced PPI use. Post-POEM TIF is safe and effective and may be a viable alternative to PPI for POEM-related GERD; however, future studies should include a control arm and post-intervention pH monitoring.

Keywords: GERD, laparoscopic Heller myotomy, peroral endoscopic myotomy, POEM, reflux, TIF, transoral incisionless fundoplication

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INTRODUCTION

Peroral endoscopic myotomy (POEM) is an established first-line endoscopic therapy for the management of achalasia with outcomes comparable[1] to surgical myotomy, with a lower rate of procedural adverse events. However,

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post-POEM gastroesophageal reflux disease (GERD) has been a major concern, with rates of documented GERD following POEM at least double[2] those of surgical myotomy. While proton pump inhibitor (PPI) therapy is a safe and effective therapy for post-POEM GERD, concerns with adherence to long-term therapy and the risk of esophagitis off therapy have prompted a search for alternatives. Transoral incisionless fundoplication (TIF) is an effective, minimally invasive modality for the management of GERD in patients with no or small (<2 cm) hiatal hernias.[3] More recently, TIF following POEM has been described in small retrospective studies[4] and shown to be technically feasible with encouraging outcomes. We conducted a prospective, patient-driven, pilot study, in which consenting patients undergoing POEM underwent protocolized GERD follow-up and were offered TIF as an alternative to long-term PPI therapy for post-POEM GERD.

PATIENTS AND METHODS

This was a single-center, pilot, prospective study of patients who underwent POEM for achalasia at Baylor St. Luke's Hospital in Houston, Texas. The study enrollment extended from April 2021 through September 2022 and included consecutive patients who at the time of POEM agreed to complete structured, objective GERD testing post POEM. Those who had objective evidence of GERD and were appropriate candidates (hiatal hernia <2 cm) were offered TIF as an alternative to long-term PPI therapy. The study was approved by the Baylor College of Medicine Institutional Review Board (IRB #H-48496) and registered at ClinicalTrials.gov under NCT04770441.

Study outcomes and definitions

The primary outcome was the percentage of patients undergoing TIF who were able to reduce or discontinue PPI therapy at 3 months post-procedure. Secondary outcomes included improvements in GERD health-related quality of life (GERD-HRQL) scores, technical success of the TIF 2.0 procedure, and adverse events. The diagnosis of GERD following POEM was established based on the presence of Los Angeles (LA) Grade B or greater esophagitis on upper endoscopy (EGD) or abnormal acid exposure (>6%) on wireless capsule esophageal pH testing.

Procedural technique

All patients underwent POEM after documentation of achalasia on high-resolution esophageal manometry. All POEM procedures were performed by two endoscopists (MO and SJ) with a combined experience of 300 POEMs, while the TIF procedure was performed by a third endoscopist (KP) with an experience of 130 TIFs. POEM was performed in standard fashion [Figure 1] using an anterior approach with the patient in the supine position. Tunnel entry was created approximately 10 cm above the gastroesophageal junction, after which tunneling toward gastroesophageal junction (GEJ) was performed and extended 2 cm beyond the cardia, followed by a full-thickness myotomy extending from 5 to 8 cm in length above the gastroesophageal junction, with final complete closure of the mucosal defect using hemoclips. TIF was performed using the Esophyx Z device (Endogastric Solutions, Redmond, Washington, USA) [Figure 2]. The device was loaded onto a gastroduodenoscope and advanced through the mouth into the stomach. Once the tissue mold was in the appropriate position, the device was used to deploy fasteners along the gastroesophageal junction at the 1 o'clock, 11 o'clock, 5 o'clock, and 7 o'clock positions in standard fashion. A total of 25-35 fasteners were deployed in total to create a 270-degree partial fundoplication.

Follow-up

Enrolled patients were contacted by telephone for follow-up at 1-, 3-, 6-, and 12-month intervals post-POEM to document PPI use and GERD-HRQL scores. All patients underwent objective GERD testing at 3 months post-POEM, and those with documented GERD after POEM as defined above were offered TIF. The decision to continue long-term PPI-only therapy or to proceed with TIF was at the patients' discretion by design. Patients were then followed for 3 months post-TIF to assess clinical response.

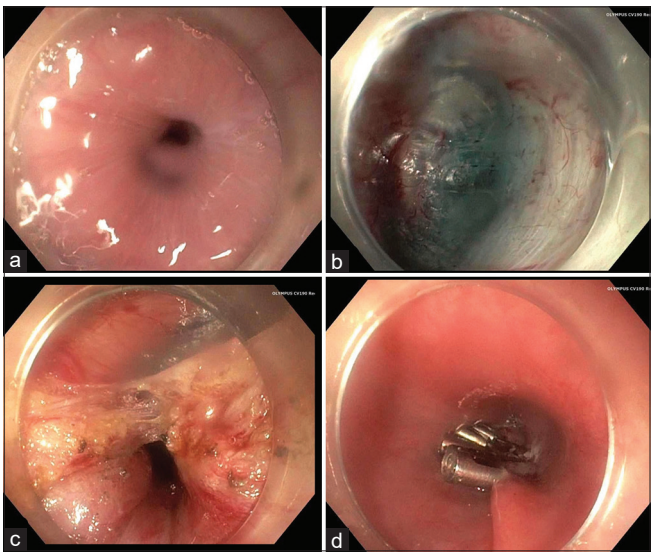

Figure 1: Peroral endoscopic myotomy (POEM) procedure. (a) "Rosette" sign at the gastroesophageal junction in a patient with achalasia, (b) tunneling through the submucosal layer of the esophagus, (c) full thickness myotomy, and (d) closure of the mucosal entry site

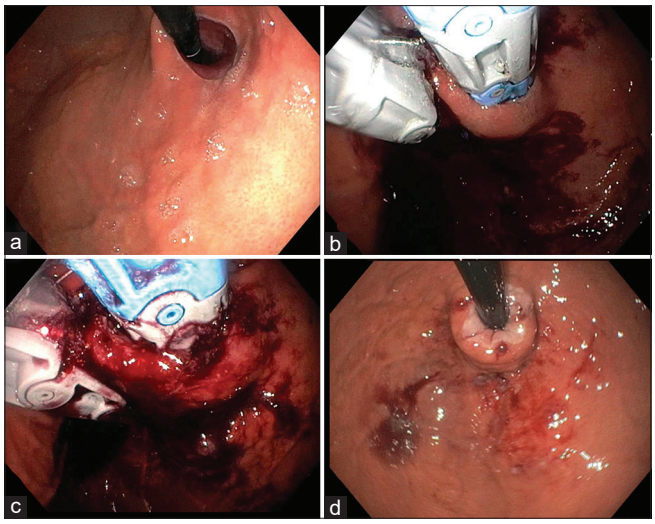

Figure 2: Transoral incisionless fundoplication (TIF) procedure. (a) gastroesophageal junction on retroflexion with a Hill Grade II valve, (b and c) TIF device during plication, and (d) Reconstructed gastroesophageal flap valve following TIF

Statistical analysis and sample size

This was a pilot study, with enrollment continuing for the duration of the study specified above. The paired T-test was used to compare GERD-HRQL scores for patients before and after TIF, and the student T-test was used to compare non-paired parametric continuous values. A $P < 0.05$ was considered statistically significant and all tests were two-tailed. Stata version 15.0 (Stata Corp, College Station, TX) was used for all statistical analyses.

RESULTS

Baseline patient characteristics

In total, 21 patients were enrolled and all underwent post-POEM objective testing for GERD. The mean patient age was 47 ± 15.6 years, and 14 patients (66.6%) were female. The mean basal metabolic index (BMI) was 31.3 kg/m^2 ± 8.1. The mean pre-POEM Eckardt score was 6.4 ± 2.3. Overall, 16 patients (76%) had type II achalasia, 2 had type I achalasia (9.5%), 1 had type III achalasia (5%), and the remainder had achalasia without a type specified.

POEM procedural characteristics and outcomes

All patients underwent POEM using an anterior approach. The mean length of esophageal myotomy was 8.2 cm ± 2 cm, and the mean length of gastric myotomy was 2.1 cm ± 0.3. There were no procedural or post-procedural adverse events. Mean post-POEM Eckardt scores are summarized in Table 1.

GERD-related follow-up

All 21 patients underwent post-POEM EGD. EGD was normal in five patients and remarkable for LA classification grade A, B, and C esophagitis in 5, 7, and 4 patients, respectively. Patients most frequently had a Hill Grade II gastroesophageal flap valve (n = 12), followed by Grade III (n = 4), and finally Grade I (n = 3), with two patients without documentation of flap valve status. Of these 21 patients, 15 patients underwent wireless capsule esophageal pH testing. Mean reported Demeester score was 19.64 ± 26.59. Of the six patients without wireless capsule esophageal pH testing, four had LA Grade B esophagitis or greater on EGD obviating the need for pH testing, one had a high GERD-HQRL score while the last did not have any clinical or endoscopic evidence of GERD. Overall 11 patients (52%) had objective evidence of GERD. Eckardt scores, PPI use, and GERD-HQRL scores for patients completing 1, 3, 6, and 12-month follow-up are reported in Table 1.

Table 1: Summary of Eckardt, GERD-HQRL scores, and PPI use in patients* completing follow-up

	1-month (n=15)	3-months (n=10)	6-months (n=9)	12-months (n=4)
Eckardt score	0.6±0.9	0.5±0.7	1±2.3	2±1.8
GERD-HQRL	4.1±6.5	4.7±7.4	5.3±14.9	5.7±5.3
PPI Use	80%	72.7%	66.7%	75%

*Excludes four patients who ultimately underwent TIF to avoid confounding

POEM-TIF outcomes

Of the 11 patients with objective evidence of GERD [Figure 3], one had a large hiatal hernia and was referred for surgical fundoplication. Of the remaining 10, all were offered TIF and four (40%) patients elected to proceed, with TIF ultimately completed at an average of 10.5 months after POEM [Table 2]. Technical success was achieved in all cases. All four patients completed subsequent 3-month follow up. Three of four patients (75%) achieved either dose reduction or discontinuation of PPI after TIF (two stopped PPI and one reduced dose in half) while one patient did not achieve a reduction in PPI dose. Mean GERD-HQRL at 3 months post-TIF (n = 4) was 3.75 ± 6.2, compared to 4.5 ± 4.5 in patients on PPI therapy, 3 months post-POEM, P = 0.815. In those who underwent TIF, mean GERD-HQRL pre-TIF (at 3 months post-POEM) was 20 ± 18.5 compared to 3.75 ± 6.2, at 3 months post-TIF (P = 0.239).

DISCUSSION

In this prospective, patient-driven, pilot study of post-POEM GERD patients, 40% of patients with objective evidence of GERD opted to undergo TIF

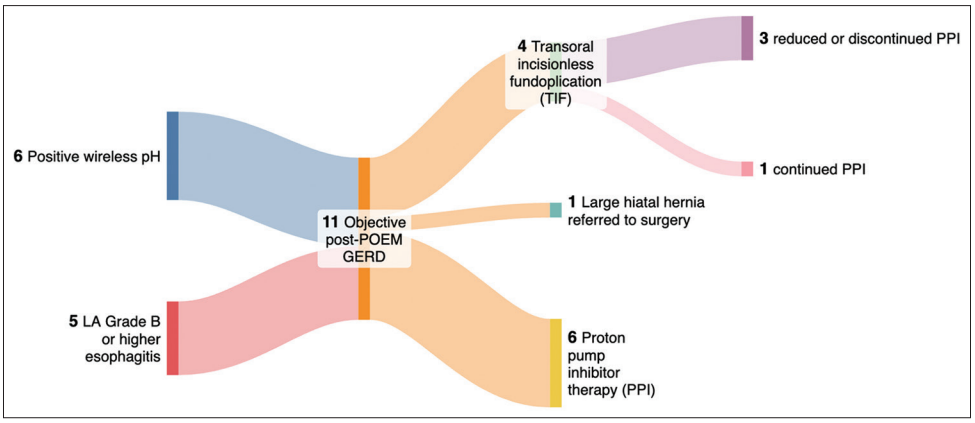

Figure 3: Sankey diagram demonstrating the flow of post-POEM patients with objective evidence of gastroesophageal reflux disease (GERD)

and most (75%) were able to discontinue or significantly decrease PPI therapy. TIF was safe and well-tolerated, and led to comparable improvements in GERD-HRQL scores compared to PPI therapy. To our knowledge, this is the first prospective study of a patient-driven management approach for post-POEM GERD with TIF being systematically offered as a therapeutic option versus long-term PPI. Our findings suggest that a sizeable portion of patients with objective GERD may select TIF as their management approach of choice and that TIF post-POEM is safe and effective and may be a viable alternative to long-term PPI therapy.

Post-POEM, GERD and associated erosive esophagitis are common and represent a significant area of concern for both patients and physicians treating achalasia. In a meta-analysis of 1542 and 2581 patients undergoing POEM and laparoscopic Heller myotomy (LHM), respectively, Repici *et al*.[2] reported that the pooled rate of abnormal acid exposure after POEM was 39% compared to 16.8% after LHM. In another meta-analysis by Schlottmann *et al*.,[5] POEM was associated with a 9.31 odds ratio for the development of erosive esophagitis compared to LHM. Out of 21 patients undergoing post-POEM objective GERD testing, we found 11 (52%) with objective evidence of GERD. Our findings are comparable to reported rates in the literature: a study of 26 patients undergoing wireless pH testing by Jones *et al*.[6] found that 58% had abnormal acid exposure. Similarly, a study of 103 POEM patients undergoing pH testing by Familiari *et al*.[7] found abnormal acid exposure in 52 (50.2%) patients.

Given these high rates of GERD following POEM, several approaches have been adopted for its management. A common approach involves performing wireless capsule pH testing for all patients post-POEM. Those with objective evidence of GERD would be offered medical or surgical therapy (i.e., fundoplication), while those without are offered surveillance off therapy. More recently, endoscopic fundoplication following POEM (termed POEM-F) was described by Inoue *et al*.[8] with encouraging results. While promising, POEM-F remains a niche procedure, requiring extensive technical expertise in natural orifice transluminal endoscopic surgery (NOTES), and is available at limited centers worldwide.

Despite the effectiveness of long-term PPI therapy for post-POEM GERD, patients frequently do not desire such long-term therapy and some may have difficulty with adherence. Additionally, some patients may rather avoid

Table 2: Patient characteristics and follow-up information in the four patients who underwent TIF post-POEM

Age/ Gender	BMI	Indication for POEM	Pre-POEM Eckart Score	Myotomy length (cm)	LA Grade esophagitis on follow-up EGD	One month post-POEM (GERD-HQRL/ PPI dose)	Six months post-POEM (GERD-HQRL/ PPI dose)	Months between POEM and TIF	Number of fasteners	Length of hospital stay post TIF	3 months post TIF (GERD-HQRL/ PPI dose)
69/F	21.4	Type II achalasia	4	12	C	4/40mg omeprazole QD	17/40mg omeprazole QD	10	28	1	0/off PPI
39/F	36.8	Type II achalasia	8	12	B	0/20 mg esomeprazole BID	23/20 mg esomeprazole BID	15	34	2	13/20 mg esomeprazole BID
48/F	23	Type II achalasia	5	8	C	0/40 mg omeprazole BID	10/40 mg omeprazole BID	10	30	0	2/off PPI
63/M	29.8	Type II achalasia	7	12	C	0/40mg pantoprazole QD	47/40mg Daily	7	28	2	0/20 mg omeprazole QD

F=female, M=male, QD=daily, BID=twice a day, EGD=upper endoscopy, NA=not available

surgical fundoplication, particularly since their original choice of POEM over Heller's myotomy may have been driven by a desire to avoid a surgical approach to the management of their disease. TIF offers a minimally invasive alternative to surgical fundoplication in patients with no or small (<2 cm) hiatal hernia. The safety and efficacy of TIF in patients with GERD has been demonstrated in several randomized controlled trials.[3,9,10] A meta-analysis[11] of eight studies with 418 patients who underwent TIF showed excellent long-term outcomes at a mean of 5.3 years of follow-up, with 53% of patients off PPI and 75.8% on occasional PPIs. Given these encouraging outcomes, TIF following POEM has recently been explored. The addition of TIF to POEM was first described by Tyberg *et al*.[12] in five patients with a 100% technical success rate and all patients discontinuing PPI use. This was more recently followed by a multi-center retrospective study by Brewer Gutierrez *et al*. pooling data from 12 patients from four US institutions with a significant decrease in the number of patients on twice daily PPI and GERD-HRQL scores.[4] Our findings are overall comparable to the broader literature on the outcomes of TIF for GERD in both POEM and non-POEM patients, with 75% of our patients reducing or completely stopping PPI therapy at 3 months. The impact of an anterior myotomy on the anti-reflux barrier is not well understood. Possible contributing factors to post-POEM GERD include loss of LES tone, flattening of the Angle of His, and de novo formation of a hiatal hernia. TIF is primarily effective in restoring the GE flap valve function of the anti-reflux barrier; however, residual GERD in some post-TIF patients points to the complex pathophysiology. Future studies on tailoring the myotomy approach to minimize GERD and modifying the standard TIF procedure to match the specific post-POEM pathophysiology are required.

While small, to our knowledge, our study is the first to prospectively study a patient-driven management approach for post-POEM GERD, that per protocol includes TIF as a therapeutic option. Our findings are overall positive, with elimination and/or significant decreases in PPI use in 75% of patients undergoing TIF, and low GERD-HRQL scores. However, it is important to recognize the limitations of our study. First, the analysis may be affected by selection bias, since the decision to proceed with TIF versus PPI therapy was patient-driven, rather than physician-driven. It is possible that the most symptomatic patients sought to proceed with TIF. In addition, patient follow-up was done via validated GERD questionnaires, but not with pH monitoring, since many patients find this cumbersome. Future analyses would benefit from a more objective post-procedural monitoring approach, which includes pH monitoring. Finally, it is important to recognize that the TIF device and associated procedure represent additional costs, and while TIF is cost-effective compared to long-term PPI in a recent analysis,[13] this was not in a post-POEM population.

In conclusion, in this patient-driven, prospective, pilot study, 40% of patients with objective evidence of GERD post-POEM elected to have TIF and 75% of those stopped or significantly reduced PPI use. Post-POEM TIF was safe and effective and may be a viable alternative to long-term PPI. Future studies would benefit from a randomized design, as well as protocolized post-TIF wireless capsule pH monitoring to document objective GERD resolution.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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