Single-session endoscopic fundoplication after peroral endoscopic myotomy (POEM+F) for prevention of post-gastroesophageal reflux – 1-year follow-up study

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ABSTRACT
Background Peroral endoscopic myotomy (POEM) is an established treatment for achalasia cardia; however, post-POEM gastroesophageal reflux (GER) remains a significant problem. Concomitant endoscopic fundoplication following POEM (POEM+F) was recently described to reduce post-POEM GER. This single-center study reports short-term outcomes of POEM+F.

Methods This was a retrospective analysis of a prospectively maintained database of patients undergoing POEM+F. Abstracted data included demographics, achalasia type, pre-POEM Eckardt score, prior therapy, follow-up. Follow-up assessment was 3-monthly for 1 year and included post-POEM Eckardt score, GerdQ score, wrap integrity and esophagitis on esophagogastroduodenoscopy, and pH studies. GER was defined according to Lyon Consensus.

Results 25 patients underwent POEM+F (mean age 40.1 years [standard deviation (SD) 13.7]; 12 females). POEM+F was technically successful in 23/25 (92.0%). Significant dysphagia improvement was seen in all 25 patients (mean pre- and post-POEM Eckardt scores 8.21 [SD 1.08] and 0.1 [SD 0.3], respectively; \( P = 0.001 \)). Mean total procedure and fundoplication times were 115.6 (SD 27.2) minutes and 46.7 (SD 12.4) minutes, respectively; times reduced significantly after the initial five cases. Median follow-up was 12 months (interquartile range [IQR] 9–13). Intact wrap was seen in 19/23 (82.6%). GER (abnormal esophageal acid exposure time [EAET]) was seen in 2/18 (11.1%) and there was one reported GerdQ > 8. Borderline GER (asymptomatic grade A esophagitis, normal EAET) was identified in 4/22 (18.2%). Three (12.0%) minor delayed adverse events occurred but required no intervention.

Conclusions POEM+F was safe and reproducible. At 12 months’ follow-up, incidence of post-POEM+F GER was low and acceptable.

Introduction
Peroral endoscopic myotomy (POEM) is an accepted treatment modality for achalasia cardia [1–4]. Results of POEM have demonstrated excellent medium- and long-term success rates [4–6]. The procedure is minimally invasive, has an excellent safety profile, and can be performed even in cases of prior treatment failure [7]. Results of POEM are superior to single-session endoscopic balloon dilation (EBD) and are comparable to laparoscopic Heller myotomy (LHM) [8,9]. However, in recent years, there has been increasing concern about post-POEM gastroesophageal reflux (GER) [10–13]. All treatment modalities for achalasia cardia induce loss of control of the lower esophageal sphincter, and are therefore prone to post-procedure GER. Conventional teaching recommends that LHM is always combined with partial or full 360° fundoplication (LHM+F), more often anterior (Dor fundoplication), to protect against postoperative GER; overall reported post-LHM+F GER rates have been acceptable [14–16].
To date, fundoplication has not been standard after POEM. Early results of POEM reported low GER rates (6%–21%) [5, 6, 17], possibly due to selection bias and limited follow-up data without objective evidence such as pH studies [4]. Recent studies have reported high incidence of post-POEM GER (15%–88%) [10–12, 18]. A recent meta-analysis reviewing POEM, LHM, and EBD demonstrated that POEM had the highest efficacy for relief of dysphagia but also the highest incidence of post-POEM GER [19]. A prospective randomized trial comparing POEM with LHM also demonstrated high incidence of post-POEM GER [10]. Although most post-POEM GER occurrences are mild (grade A or B), severe GER (grade C or D) or development of Barrett’s esophagus has also been reported [10, 12, 20, 21]. Currently, most POEM centers recommend long-term endoscopic surveillance to identify such changes [22, 23].

In an attempt to reduce post-POEM GER, Inoue et al. described a novel endoscopic fundoplication following anterior POEM, either as a single-stage concomitant procedure (POEM + F) or later as a separate subsequent procedure (POEF) [24, 25]. The procedure aimed to replicate surgical (laparoscopic) or later as a separate subsequent procedure (POEF) [24, 25]. A recent meta-analysis reviewing POEM, LHM, and EBD demonstrated that POEM had the highest efficacy for relief of dysphagia but also the highest incidence of post-POEM GER [19]. A prospective randomized trial comparing POEM with LHM also demonstrated high incidence of post-POEM GER [10]. Although most post-POEM GER occurrences are mild (grade A or B), severe GER (grade C or D) or development of Barrett’s esophagus has also been reported [10, 12, 20, 21]. Currently, most POEM centers recommend long-term endoscopic surveillance to identify such changes [22, 23].

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documentation of GER. Both EGD and pH studies were performed in patients following a minimum of 1 week off PPI medication.

Subsequent follow-up was by periodic telephone standardized questionnaire at 3, 6, 9, and 12 months post-procedure to assess Eckardt and GerdQ scores. Patients experiencing symptomatic GER and with evidence of erosive esophagitis or abnormal esophageal acid exposure time (EAET) were recommended long-term PPI therapy.

Outcome assessments and definitions

The primary outcome of the study was the incidence of significant post-POEM + F GER. Secondary outcomes were clinical resolution of dysphagia, development of intraprocedural or delayed adverse events, and integrity of the wrap at follow-up.

Technical success was defined as successful completion of POEM + F. Clinical success was defined as resolution of dysphagia as determined by post-procedure Eckardt score ≤ 3 and absence of post-POEM + F GER. Post-POEM + F GER was defined according to the Lyon Consensus as EAET > 6% on pH studies or endoscopic evidence of Grade C or D esophagitis. Presence of Grade A or B esophagitis and EAET 4%–6% was considered as borderline evidence [27]. Presence of significant GER symptoms (GerdQ score ≥ 8) was recorded [28]. Adverse events were defined according to the American Society for Gastrointestinal Endoscopy lexicon for endoscopic adverse events [29].

Statistical analysis

Continuous variables were recorded as mean and standard deviation (SD) or median and interquartile range (IQR), and categorical variables were recorded as counts and percentages. A P value of <0.05 was considered statistically significant. Wilcoxon sign rank test was used to calculate the P value. All statistical analyses were computed using SPSS software version 22 (IBM Corp, Armonk, New York, USA).

Results

During an 11-month period (March 2019 to January 2020), 25 of 36 patients with achalasia cardia underwent POEM + F. The patient recruitment, procedure, and follow-up algorithm is detailed in **Fig. 1** in the online-only Supplementary material. A total of 11 patients were only offered standard POEM because they were unsuitable for POEM + F (5 patients had post-LHM recurrent achalasia, 4 patients were high risk for anesthesia [ASA Class III or higher], 1 patient refused consent, and another pa...
tient had severely tortuous sigmoid achalasia for which POEM was anticipated to be technically difficult and time consuming, and therefore POEM+F was considered unsuitable because it was likely to prolong the procedure time significantly.

Baseline demographics and clinical characteristics of patients are summarized in Table 1. Mean age was 40.1 (SD 13.7) years and there were 12 females. Mean duration of symptoms before POEM+F was 12.7 (SD 10.2) months. A total of 23 patients (92.0%) had type II achalasia cardia, whereas type I and type III achalasia cardia were only seen in one patient each. Two patients had recurrent achalasia cardia after prior failed EBD. All other 23 patients (92.0%) were naïve achalasia cardia. Mean pre-procedure Eckardt score was 8.21 (SD 1.08).

Perioperative characteristics and outcomes are detailed in Table 1. Although POEM was successful in all patients, POEM+F was successful in 23/25 patients (technical success 92.0%). In two patients, fundoplication could not be performed after POEM due to device failure in one patient (breaking of the endoloop after fixation while tightening) and unfavorable anatomy in the other (sliding hiatal hernia with thick perigastric pad of fat). Mean and median total procedure times for POEM+F were 115.6 (SD 27.2) minutes and 105 (IQR 90–270) minutes, respectively, of which mean 46.7 (SD 12.4) minutes and median 45 (IQR 35–90) minutes were additionally required for fundoplication. The moving average curve demonstrated significant improvement in total procedure time after the first five procedures (88 [SD 23.4] minutes for first five cases vs. 51.2 [SD 9.1] minutes for subsequent cases; P < 0.05) (Fig. 2s). No intra- or immediate post-procedure adverse events related to POEM+F were encountered. Mean post-procedure hospital stay was 2.1 (SD 0.5) days.

Clinical follow-up was available for all 25 patients. Median duration of follow-up was 12 months (IQR 9–13). Significant improvement in dysphagia was seen in all patients (mean post-procedure Eckardt score 0.1 [SD 0.3] vs. mean pre-procedure score 8.21 [SD 1.08]; P = 0.001) (Table 1).

GER was evaluated in 23 patients who underwent successful POEM+F (Table 2). Two patients who underwent only POEM were excluded from the GER evaluation. GERQ scores for all 23 patients were obtained at a median of 12 months (IQR 9–13) after POEM+F. Scores were < 8 in 22/23 patients (95.7%) signifying low probability of GER [28, 30]. Regular PPI use was not reported by any patients. Post POEM+F 24-hour pH studies were obtained in 18/23 patients (78.3%) at a median of 2 months (IQR 1.5–6.75). All pH studies were performed with patients after 1 week off PPI. DeMeester scores and EAET were positive for GER in 2 patients (11.1%) (EAET > 6%) whereas these values were normal in the remaining 16 patients (88.9%) (EAET < 6%). The symptom index demonstrated 100% and 80% correlation, respectively, in the two patients with positive scores. For the remaining 16 patients, mean EAET was 1.12 (SD 0.7). Meaningful symptom index calculation could not be performed in these patients due to the low values.

Follow-up EGD was performed in 22 patients (95.7%) at a mean of 2.78 (SD 3.54) months post-procedure (median interval 1.5 months, IQR 1–2). All EGDs were performed after patients had been off PPI for at least 1 week. One patient refused EGD because of lack of symptoms. EGD revealed an intact wrap in 19/22 patients (86.4%) (Fig. 2a). The wrap was not distinctly visible (indistinct) in two patients (Fig. 2b), whereas it appeared loose with an open lower esophageal sphincter in one patient (Fig. 2c). Overall, the wrap was found to be intact in 19/23 patients who underwent successful POEM-F (82.6%). Erosive esophagitis (Grade A) was seen in 4/22 patients (18.2%), two of whom had an indistinct wrap. Notably, all four patients had normal EAET and DeMeester scores, and none reported GER symptoms.

Three delayed adverse events were reported (12.0%): EGD revealed that an endoclip (one patient) and the cut ends of the endoloop (two patients) had eroded through the mucosa overlying the submucosal tunnel in the distal esophagus or at the gastroesophageal junction. In all three patients, surrounding...
esophageal mucosa had completely healed around the clip or loop without any residual visible mucosal breach. No patient reported any directly attributable symptoms to these findings.

Follow-up of the two patients with failed POEM+F revealed an elevated GerdQ score and Grade B esophagitis in one patient, whereas the other patient was asymptomatic and did not have erosive esophagitis on EGD. Both patients did not undergo pH studies. Long-term PPI was prescribed to the patient reporting GER.

Post-POEM+F GER as per the Lyon Consensus was identified in two patients (11.1%; 95% confidence interval 10.6–11.5). One of these patients had a loose wrap on EGD and was also significantly symptomatic (GerdQ score 11). Neither patient demonstrated erosive esophagitis on EGD. Borderline evidence of GER as evidenced by Grade A esophagitis was additionally observed in four patients but pH studies and symptom scores were all normal (Table 2s).

### Discussion

Although POEM is a well-established treatment modality for achalasia cardia [1–3], post-POEM GER has been a significant challenge in recent years [10–12, 18]. POEM has therefore been criticized by surgical experts and several other sources [10–13]. Post-POEM GER is often asymptomatic, may remain undiagnosed, and surveillance endoscopies and long-term PPI have been recommended for all post-POEM patients [23]. Long-term effects of such GER are largely unknown, but occasional reports of post-POEM Barrett’s esophagus and cancer have raised significant alarm [31].

In comparison, LHM – the surgical counterpart of POEM – has always incorporated a partial or complete 360° fundoplication as an integral part of the surgical procedure. The addition of fundoplication to LHM has demonstrated significant reduction in the incidence of post-operative GER [16, 32, 33]. GER in post-LHM+F patients is significantly less frequent compared with that after POEM [19, 21].

Based on the principle of LHM+F, Inoue et al. reported POEM+F and POEF as endoscopic antireflux procedures following POEM [24]. The fundoplication wrap in POEM+F closely mimics the Dor partial fundoplication – a standard recommended procedure following LHM. The initial series of Inoue et al. included 21 patients and reported safety, feasibility, and short-term outcomes following POEM+F; results demonstrated an intact wrap in 95% of patients at 1-month follow-up. The current study reports short-term outcomes following POEM+F. POEM was effective in all 25 patients as evidenced by significant improvement in dysphagia and pre- and post-POEM Eckardt scores, whereas POEM+F was successful in 23 patients (92.0%).

The primary aim of this study was to calculate the incidence of significant post-POEM+F GER. Our results demonstrate that significant GER (EAET>6%) was documented in only 2/18 patients (11.1%) with excellent symptom index correlation. This is much lower than that documented in other POEM studies [10–12, 18]. These results are promising and suggest that POEM+F could protect against post-POEM GER, although additional studies are required to confirm these results.
Wrap integrity at follow-up was another parameter assessed during the current study. The wrap appeared to be intact in 19 patients (82.6%) at follow-up EGD at a median of 1.5 months. POEM + F is based on surgical principles that depend on tissue healing, fibrosis, and adhesion formation to maintain wrap integrity. As tissue healing is usually completed by 6 weeks, it is likely that a wrap intact at 6 weeks will maintain integrity in the long term. The wrap was loose in one patient (abnormal EAET > 6% and elevated GerdQ score confirming GER) and indistinct in two patients (both reported Grade A esophagitis). It is therefore important to note that all three patients with wrap failures had either conclusive or borderline evidence of GER on follow-up evaluation. On the other hand, the fact that all 19 patients with an intact wrap reported normal GerdQ scores at a median of 12 months’ follow-up suggests that the wrap could be an effective barrier against GER.

Grade A erosive esophagitis was found in four patients, two of whom had wrap failure whereas it was intact in the other two. However, as GerdQ scores and EAET were normal in all four patients, it is impossible to determine whether the esophagitis was due to GER or food stasis.

Diagnosis of post-POEM GER is challenging, and the guidelines presented by the Lyon Consensus are possibly most relevant in this regard [27]. The results of the present study demonstrate conclusive evidence of GER in 11.1% patients and if both conclusive and borderline evidence were to be considered – 26.1%. Of these, only one patient was symptomatic (1/23, 4.3%), four had endoscopic evidence (4/22, 18.2%), whereas EAET was abnormal in 2/18 (11.1%). In comparison, symptomatic post-POEM GER has been reported in 19%, by pH studies in 39%, and on endoscopy in 29.4% in a recent large meta-analysis [11]. It appears, therefore, that POEM + F could be protective against post-POEM GER.

Fundoplication has been a standard procedure for prevention of postoperative GER after LHM. In a large meta-analysis of 64 articles reporting outcomes of 4871 LHM + F procedures, Campos et al. reported a mean postoperative GER incidence of 8.8% (range 0–44) [16]. The current study demonstrated 11.1% post-POEM + F GER incidence, which is comparable to that reported for LHM + F. Further validation by larger randomized studies is necessary to confirm these findings.

Is POEM + F reproducible? We previously reported an initial series of four patients undergoing successful POEM + F [26]. Further to this, the current series reported 92.0% (23/25) technical success of POEM + F. No intraoperative adverse events were encountered, although technical failures occurred in two patients. In the first patient, the endoloop snapped while tightening the wrap, possibly owing to friction from an endoclip. Although it was technically feasible to redo the fundoplication using a new endoloop and clips, we preferred not to pursue this in the interest of patient safety owing to the increased anesthesia time that would be required. The other patient had a sliding hiatal hernia with an angulated anatomy at the gastroesophageal junction, and a thick pad of fat at the point of entry into the peritoneal cavity. Dissection and entry into the peritoneal cavity and subsequent visualization was considered difficult and could likely compromise procedural safety. Fundoplication was therefore aborted to avoid inadvertent intraperitoneal injury or adverse events. Both these patients were among our initial five patients when experience with this technique was limited. No technical challenges were encountered in the remaining 23 patients. Additional operative time was necessary to perform POEM + F; however, the learning curve was identified to be short (five cases). POEM + F can therefore be considered a safe procedure with acceptably low failure rates, and these may further reduce with increased experience.

Delayed adverse events were reported in our study, involving a clip or endoloop tail eroding through the mucosa in three patients (12.0%); no other adverse events were encountered. No endoscopically visible mucosal breach was identified in any of these patients and the mucosa had completely healed around these inclusions. Patients had no related symptoms and therefore these findings have doubtful clinical significance.

Currently no consensus exists regarding the optimal approach for the prevention of post-POEM GER. Most patients are maintained on PPI with good symptom control [34]. Endoscopic antireflux procedures have been reported to be used in conjunction with POEM in an attempt to reduce post-POEM GER. Tyberg et al. reported a series of five patients treated with second-session transoral incisionless fundoplication performed after POEM, which demonstrated impressive short-term results [35]. The same group then also reported a single-session approach in a solitary case report [36]. Toshimori et al. reported on POEF (POEM + F performed over two independent sessions) as a subsequent second procedure to control post-POEM GER [25]. The authors also demonstrated use of endoscopic suturing instead of endoloop and clips to create the wrap. It will be interesting to evaluate which of these techniques can provide a more robust and secure fundoplication in the long term.

Although the two-session approaches are plausible alternatives, they have the inherent drawback of requiring two separate procedures, thereby increasing procedure costs, invasiveness, and potential morbidity. They may therefore be less preferred to POEM + F or LHM + F in routine practice. In contrast, POEM + F offers the advantage of a single-session fundoplication akin to what is practiced and recommended for surgical myotomy. The procedure is also less device dependent, and therefore costs are likely to be lower. Although it may be argued that not all POEM patients develop GER and therefore an antireflux procedure may not be required in all, the reported high incidence of post-POEM GER (especially asymptomatic GER), along with the fact that fundoplication has been a standard procedure following LHM for several decades, surely justify the approach of single-session POEM + F. Laparoscopic fundoplication has also been described after POEM to treat post-POEM GER [34]. Although effective, this approach defeats the primary purpose of performing a less-invasive procedure such as POEM if a more invasive approach is later required to control its side-effects.

The current study has several limitations. First, it was a retrospective case series from a single center, and therefore these results need confirmation in larger multicenter trials. Second, nearly one-third of eligible patients (11/36, 30.6%) were not of-
ferred POEM+F, and therefore possible bias exists regarding pa-
tient selection. Third, although clinical follow-up was obtained
in all patients, follow-up EGD and pH studies could not be ob-
tained for all. It is possible that asymptomatic GER could have
been missed in these patients. Furthermore, we understand
that nonavailability of impedance pH may limit interpretation
of some of the results. Fourth, the study was a single-arm study
without a POEM-only comparator arm. Future comparative
studies will be required to address this issue. Finally, POEM+F
is an evolving procedure. It is therefore likely that with increas-
ing experience, the technique may be simplified, and that the
results and outcomes may demonstrate more solidarity in fu-
ture.

In conclusion, this single-center study demonstrated excel-
 lent short-term outcomes of POEM+F for the control of post-
POEM GER. The procedure was reproducible and safe, and the
integrity of the wrap was well maintained at follow-up. Inci-
dence of post-POEM+F GER at a median 12-month follow-up
was low and acceptable. POEM+F offers the advantage of a sin-
gle-session endoscopic solution for achalasia cardia treatment
with possible control of GER. These findings require further va-
lidation in larger randomized studies with longer follow-up.

**Competing interests**

The authors declare that they have no conflict of interest.

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