

Gastric peroral endoscopic pyloromyotomy (G-POEM) in patients with refractory gastroparesis: a review

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Abstract: Gastric peroral endoscopic pyloromyotomy (G-POEM or POP) is an endoscopic therapeutic modality for treatment of refractory gastroparesis. Since the first case reported in 2013, there are more than 200 papers published on G-POEM. In this narrative review, we summarize the short-term and long-term outcomes and review other important studies. The technical success rate is 100% and the short-term (within 1 year) success rate is about 50–80%. The procedure time is between 50 and 70 min while the average length of hospital stay was 2–3 days. The adverse event rate was around 10%. Few patients need further intervention. Three studies showed that at the 4-year follow-up, the response to G-POEM was durable, but there was a yearly recurrence rate of 13% or more. Redo G-POEM is feasible and can be of benefit for some patients. Most of the studies showed that long duration of illness is associated with poor outcomes. However, reliable predictors for successful outcomes are still unknown. Current literature indicates G-POEM is superior to gastric electric stimulator and surgical pyloroplasty. Endoflip has been used at G-POEM to predict the outcome, but the result is very preliminary. A recent sham study confirms the short-term efficacy of G-POEM. G-POEM is safe and about 50% of patients can be discharged to home on the same day. G-POEM allows for direct biopsy of the gastric muscle, which is the location of the pacemaker cells, the interstitial cells of Cajal; therefore, G-POEM may provide a new path for further research on the pathogenesis of gastroparesis.

Keywords: gastroparesis, G-POEM, myotomy, POP

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Introduction

Gastroparesis is defined as delayed gastric emptying in the absence of mechanical obstruction. The pathogenesis of gastroparesis is unknown and can include impaired gastric accommodation, autonomic neuropathy, uncoordinated gastric contractility, pyloric dysfunction, degeneration of interstitial cells of Cajal (ICC), and neurohormonal disruption.¹ Gastroparesis presents with vague symptoms of nausea, vomiting, early satiety, postprandial bloating, and abdominal pain. In severe cases, weight loss and malnutrition can occur. The most common etiologies for gastroparesis result from diabetes, surgery, or infection, but can be idiopathic. Patients presenting with

symptoms consistent with gastroparesis should undergo endoscopy to rule out obstruction and a 4-h gastric emptying study to confirm the diagnosis. Medications and dietary modifications are the first-line treatment for gastroparesis, but approximately 30% of patients do not have relief with conservative methods.² Refractory gastroparesis can be defined as gastroparesis with poor response to greater than 6 months of dietary modifications and trial of maximally tolerated doses of prokinetic medications.³ The medications are not usually used long term due to unfavorable side effects, especially tardive dyskinesia.³ With gastroparesis becoming more common along with its limited use of conservative therapy, alternative treatment

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methods for gastroparesis are becoming greatly needed.²

Alternative treatment methods include gastric electric stimulator, surgical pyloroplasty, botulinum toxin injection, and transpyloric stenting. These methods are not widely used due to invasiveness and lack of consistent results. The gastric electrical stimulator (GES) targets electrical activities that modulate gastric emptying through the ICC. ICC act as the pacemaker of the gastrointestinal system by creating slow-wave impulses toward the pylorus to promote gastric emptying. There is potential in the mechanism, but device-related complications are seen in approximately 15% of patients, with a removal rate of 6.3–12.8%.³ There may be serious adverse effects associated with this treatment including sepsis, stroke, and death.²

Atypical pylorus muscle characteristics, such as a narrow cross-sectional area (CSA) or diameter, can also contribute to gastroparesis, making pylorus-directed therapies an option for treatment. Gastric peroral endoscopic myotomy (G-POEM) is a type of submucosal endoscopy or third space endoscopy that targets the pylorus muscle to treat gastroparesis.²

G-POEM was derived from peroral endoscopic myotomy (POEM), which targets the lower esophageal sphincter to treat achalasia. These procedures use submucosal tunneling to dissect specific muscles, specifically the pylorus in gastroparesis.² The process of G-POEM involves submucosal injection, mucosal incision, submucosal tunnel creation, myotomy, and closure of mucosal entry site with clips of endoscopic suturing (Figure 1 and Video).

G-POEM was first reported on a human patient in 2013⁴ without any adverse effects and showed significant reduction in symptoms at the 12-week follow-up. Since then, many studies have been published covering mainly short-term outcomes of POEMs in single-center or multicenter studies. This review aims to examine current evidence on clinical outcomes of G-POEMs in the short term and the long term. This review also aims to compare G-POEM with alternative techniques such as gastric electrical stimulation and laparoscopic pyloromyotomy. Lastly, this review will identify G-POEM compared with a placebo and the role of G-POEM in biopsy to evaluate ICC function.

Short-term outcomes

The Gastroparesis Cardinal Symptom Index (GCSI) score is a standard tool used to estimate the severity of gastroparesis.⁵ GCSI is measured on a Likert scale with 0 being the lowest score and 5 being the highest score. There is a mean of three subscales that make up the GCSI score. The first subscale includes nausea, retching, and vomiting. The second includes stomach fullness, inability to finish a normal-sized meal, feeling excessively full after meals, and loss of appetite. The third subscale includes bloating and stomach distention. The highest possible score is 45 from all nine items, but an average score is typically used. Clinical success of a G-POEM procedure is defined as a decrease in at least 1 point in the average total GCSI score with more than a 25% decrease in at least 2 subsets of cardinal symptoms.⁶ Most of the studies use this definition or one similar to this.

More than 200 papers on G-POEM have been published since the first report in 2013. Most of these publications are reports on the short-term outcomes at a follow-up between 6 months and 1 year. There are seven systematic reviews with meta-analysis on G-POEM published.^{1,7–12} Many of the studies included in those review papers are overlapped. Two recent reviews^{1,12} included 17 studies that are the main studies on the short-term outcomes of G-POEM.^{6,13–28}

The most recent meta-analysis was done in 2021¹ and included 10 studies and 482 patients. The pooled rate of clinical success at 1 year following G-POEM was 61% and the pooled rate of adverse events was 8%. However, some of the studies included in this analysis were different types and defined clinical success differently.

Pooled clinical success rate at 1 year and pooled rate of adverse events were metrics that were evaluated in this study. There were subgroup analyses done on retrospective studies and prospective studies. The analysis of prospective studies showed a 48% success rate compared to 70% success rate in retrospective studies. The adverse event rate was similar between the subgroups, with 7% and 9% in prospective and retrospective studies, respectively.¹

Next, there were subgroup analyses done among studies that used similar definitions of clinical success. The first subgroup analysis defined

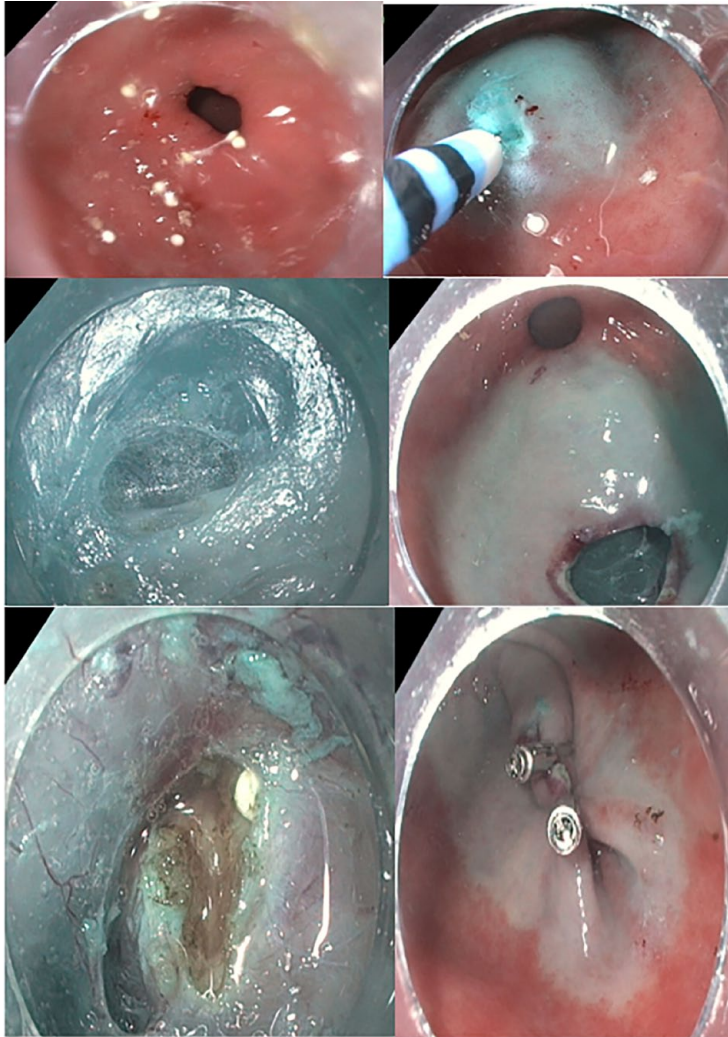


Figure 1. G-POEM procedure.

clinical success as at least a one-point decrease in the average of total GCSI score. This resulted in a clinical success rate of 50%. The next subgroup defined clinical success as at least one-score decrease in the total GCSI score with >25% decrease in at least two of the subscales. This resulted in a similar success rate of 57%.¹

The data show us that most subgroups in this study had a relatively low adverse event (<10%) with a clinical success rate of approximately 50%. There seems to be a larger reported clinical success rate when the data were studied retrospectively.¹

Significant predictors of clinical success include baseline GCSI scores higher than 2.6, baseline

gastric retention of more than 20% at 4h, and high preoperative GCSI satiety subscale score. Patients with high body mass index (BMI), psychiatric medication history, long duration of gastroparesis, or high gastric retention at 4h after G-POEM had significant predictors of clinical failure. It is important to carefully select patients to undergo G-POEM that are likely to benefit from this procedure. Although it is less invasive than surgery, there is still potential for iatrogenic damage. Future studies may consider a certain selection criterion when selecting patients that are likely to benefit from G-POEM.¹

We included all systematic review and meta-analysis studies in Table 1.^{1,7-12} Since those studies were published in a relatively short time, within

Table 1. Short-term outcomes of G-POEM in recent systematic review and meta-analysis studies.

| Reference | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|-------|---------------|--------|----------------------|----------------------|-------|--------|
| Publication year | 2019 | 2020 | 2020 | 2020 | 2020 | 2021 | 2022 |
| Number of patients | 196 | 292 | 281 | 235 | 375 | 272 | 482 |
| Number of studies (prospective studies) | 7 (2) | 10 (2) | 10 (4) | 9 (2) | 11 (1) | 8 (3) | 10 (3) |
| Mean procedure time (minutes) | 69.7 | 62.4 | 51.0 | 55.6 | 63.8 | 70.9 | N/A |
| Mean length of hospital stay (days) | 1.96 | 3.4 | 2.32 | 3 | 3.3 | 3.1 | N/A |
| Mean follow-up (months) | 1–18 | 7.8 | 7.5 | 5.4 | 7 | 7.2 | 17.5 |
| Procedure success rate (%) | 100 | 100 | 100 | 100 | N/A | 100 | N/A |
| Clinical success rate (%) | 82 | 83.9 | 71 | GCSI—81.5; GES—55 | GCSI—75.8; GES—85 | 84 | 81 |
| Mean value of GES decreased (%) | 22.3 | Significantly | 26.3 | 23.8 | 24.7 | 25.4 | 28.8 |
| Adverse events (%) | 6 | 6.8 | 18 | 12 | 11 | 12 | 8 |

the last 3 years, many studies overlap. However, based on the results in Table 1, we still can make the following conclusions: First, the technical success rate was 100% with a short-term (within 1 year) clinical success rate between 70% and 80%. In addition, the procedure time is between 50 and 70 min with a length of hospital stay of 2–3 days. Lastly, the adverse event rate was between 6% and 18%, with few needing further interventions.

Long-term outcomes

There is limited evidence on long-term outcomes of G-POEM. Determining long-term outcomes of G-POEM is imperative for wider adoption of this technique. In 2021, we first reported a study on 4-year follow-up on a retrospective case series of all patients who underwent G-POEM for refractory gastroparesis.³ Patients' quality of life was quantified using the GCSI as well as the Short Form-36 questionnaire (SF-36). The SF-36 assesses metrics of quality of life such as physical functioning, role limitation caused by emotional or health problems, bodily pain, general health, vitality, social functioning, and mental health.²⁹

In this study, 97 patients that underwent G-POEM from June 2015 to March 2019 were followed. This study defined clinical success as a decrease in at least one point in the average total

GCSI score with more than a 25% decrease in at least 2 subscales of cardinal symptoms. Overall, at a 2-month follow-up, the group had a significant improvement in gastric retention at 4h, decreasing from an average baseline of 50.6% to 20.1%.³

Between 3 and 6 months after G-POEM, 81% of patients exhibited a clinical response, with 69.1% of patients maintaining that response at the 1-year follow-up. 12.9% of initial responders per year lost their clinical response in the 12- to 36-month follow-up period.

Six of the seven patients that were still being followed in the study had a clinical response at 3 years following G-POEM. These findings suggest that the procedural benefit of G-POEM could be durable.³

G-POEM has potential for alleviations of health-care burdens caused by gastroparesis.^{3,30} In the 6 months following G-POEM, hospitalizations related to gastroparesis decreased from 8.2 to 0.7. In addition, monthly emergency room visits decreased from an average of 2 to 0.3. After G-POEM, there was a significant improvement in quality of life on SF-36 survey, with a statistically significant correlation between the clinical response and improvement in SF-36 score. Subgroup analysis showed a significant improvement in mental health, role limitation caused by

physical health, role limitation caused by emotional problems, vitality, general health, social functioning, and physical functioning.³

Nine out of 12 J-tube-dependent patients were able to tolerate oral feeds without requiring their J-tubes after G-POEM. Three out of five patients that relied on total parenteral nutrition were able to discontinue this therapy. Before G-POEM, 96% of patients were on metoclopramide and approximately 55% were on other medications, including erythromycin, domperidone, and other antiemetics. Six months following G-POEM, 59 patients (66%) discontinued their regularly scheduled antiemetics.³

This study found that longer duration of gastroparesis, higher BMI, history of psychiatric medication use, and history of pain medication use increased the odds of G-POEM failure, like the results found in studies looking at short-term effects. Four patients had adverse events – two being mild and two being moderate. There was no need for surgical intervention and no procedure-related mortality was seen, showing the relatively low-risk profile of G-POEM.³

In this study, out of all patients that had an initial clinical response to G-POEM, 13% of patients lost that response per year over the 3-year follow-up. Recurrence of gastroparesis after G-POEM cannot be explained. Two patients that experienced recurrence of symptoms following G-POEM had increased resistance of scope passage through the pylorus upon repeat upper endoscopy. These patients repeated G-POEM, which showed fibrosis at the myotomy site. Repeat myotomy resulted in regaining of clinical response for these patients.³¹ One theory for the disease process of gastroparesis is an immune response leading to fibrosis of the gastrointestinal tract, namely the pyloric myotomy site, which could explain the recurrence of symptoms.³ Two patients in this study that did not have clinical response with G-POEM underwent Roux-en-Y gastric bypass and a laparoscopic gastrectomy with relief of gastroparesis symptoms. This suggests that due to the relatively safe profile and high technical success rate of G-POEM, it could be used to categorize patients with terminal refractory gastroparesis for surgical resection once identified as non-responders to G-POEM.³

Two more papers were published online ahead of print on long-term outcomes of GPOEM.^{32,33} One of the studies established a 4-year follow-up after patients underwent G-POEM procedure. At the 4-year follow-up, there was a general clinical success of 77.5%, with patients with diabetic gastroparesis (DG) having a higher success rate of 86.5%. Different etiologies of gastroparesis are speculated to have different responses to G-POEM due to the complex and poorly understood pathophysiology of gastroparesis.³²

Nausea and vomiting have been reported in up to 60% of DG patients, which is likely due to the delayed gastric emptying and pylorospasm seen in this condition. This theory could explain why G-POEM is more successful for DG patients as the rupture of the pyloric ring would relieve symptoms of nausea and vomiting more often than those of bloating and satiety.⁶ Previous studies have showed a particular improvement in nausea and vomiting after G-POEM, and this study reestablishes this relationship.²

Gastric emptying scintigraphy (GES) shows a more prominent improved outcome in DG compared with other etiologies. However, GES normalization was rather equal among etiologies and did not have a major effect on clinical symptoms. This is in congruence with prior studies, suggesting that clinical success is a more important metric than GES results due to its objectivity. In addition, G-POEM's effect on other gastroparesis features such as fundic hypocontractility and autonomic neuropathy is not well established, particularly how it affects clinical success.²

The findings of this study ultimately found an early term clinical success of 96.7% with 77.5% at the 48-month follow-up. This is consistent with similar studies that had shorter follow-ups. Some obstacles to these studies were a significant decline in healthcare utilization and follow-up at the 12-month period and beyond. A significant decline in number of hospitalizations was observed with a decrease from 51.3% to 12.3% at 48 months.³²

In this study, clinical success at 48 months was considered as the main outcome. Certain factors correlated with higher rates of success including DG diagnosis for less than 24 months, symptoms of nausea and vomiting, GCSI of 1.5–2.5 at

6 months, and retention percentage at 4 h (RP4H) of less than 10% at 6 months. Other studies have identified additional predictive factors for both success and failure. Some predictors for failure found by other authors include female gender, diabetes mellitus, high RP4H, duration of gastroparesis for longer than 24 months, and high BMI. Some predictors for clinical success found by other authors included high preoperative GCSI satiety subscale and symptoms of nausea and vomiting. Other noteworthy correlations with clinical success are age, GCSI, and retention at 2 h. Differences in predictive factors could be attributed to definition of the outcome, type of statistical analysis performed, and the power and stability of the model. Limitations to the study include single-center study, absence of control group, and objective assessment of pyloric function.³²

The other study published online ahead of print reported clinical success rate of 65.2% at 36 months.³³ In this study, the author established a G-POEM predictive score to which points were assigned as follows: nausea subscale < 2: predictive of success, 1 point; satiety subscale > 4: predictive of success, 1 point; bloating subscale > 3.5: predictive of success, 1 point, H4 % retention on scintigraphy > 50%: 1 point (5%). A threshold of two predicted clinical success with 93.3% sensitivity (95%CI: 0.77–0.99), 56.3% specificity (95%CI: 0.33–0.77), 80% positive predictive value (PPV; 95%CI: 0.67–0.93), 81.8% negative predictive value (NPV; 95%CI: 0.59–1.00), and 80.4% accuracy (95%CI: 0.69–0.92). Patients with a score ≥ 2 were significantly more likely to be responders at 3 years than those patients with a score < 2 (80% and 18%, respectively; $p = 0.0004$).³³

We summarized all three studies on long-term outcomes of G-POEM in Table 2. Recurrence of gastroparesis occurred in all studies, but some patients maintained a clinical response and improved quality of life for as long as 4 years. Long duration of gastroparesis is associated with worse outcome of GPOEM.

Other studies

G-POEM versus pacemaker

Gastric electrical stimulation (GES) is a treatment option for medically refractory gastroparesis.

One-year clinical response rates vary from 45% to 74%, with only 25% of the initial patient group maintaining that response at the 3-year follow-up. The mechanism of GES is thought to be mediated by the enteric nervous system, autonomic nervous system, or *via* a direct central nervous system effect. One proposed mechanism is that stimulation of the nausea and vomiting center of the brain leads to symptomatic improvement.^{34–39}

GES is invasive and involves risks such as implantation site pain, infection, dislodgement, and skin erosion. Other adverse effects include destruction of stomach innervation, ICC, and fibrosis of the muscular layer of the pylorus. These effects could diminish clinical response in patients that undergo GES. There is an associated removal rate of 6.3–12.8%. Device-related adverse events occurred in 13% of patients that underwent GES.^{34–39}

When compared to GES, G-POEM is less invasive with higher 1-year clinical response rates of 57–85%. G-POEM has shown to be effective for patients with medically refractory gastroparesis who have failed GES.⁴⁰ In a propensity score-matched study published in February 2020 with a median follow-up of 27.7 months, G-POEM showed a 60% lower risk of clinical recurrence than GES. In this study, clinical recurrence of gastroparesis was defined as symptoms that were refractory to medical management, required one hospitalization related to gastroparesis, and persistent GCSI score of ≥ 3 for at least 6 months.⁴¹

G-POEM showed improvement in symptoms in all etiologies of gastroparesis, and GES had little effect on idiopathic gastroparesis. Therefore, results from multiple studies show that patients with idiopathic gastroparesis are not ideal candidates for GES. G-POEM and GES have similar symptomatic relief for patients with non-idiopathic gastroparesis.

Safety of G-POEM is consistent among current studies, especially when compared to GES. GES has a significant percentage of device-related adverse effects and removal rate. There was a higher proportion of G-POEM patients requiring more frequent and longer hospital stays following the procedure when compared to GES. This could be due to monitoring of the patient for potential adverse effects.⁴¹ Up to 20% of patients experience complications following GES that may include infection, migration, erosion of the

Table 2. Long-term outcomes of G-POEM.

| Reference | Long term 1 | Long term 2 | Long term 3 |
|---|---|---|--------------------------------------|
| Publication year | 2021 | 2022 | 2022 |
| Length of follow-up (years) | 3 | 4 | 3 |
| Number of patients | 97 | 374 | 66 |
| Number of patients at study conclusion | 7 | 102 | 46 |
| Clinical success rate at study conclusion (%) | 85.7 | 77.5 | 65.2 |
| Adverse events (%) | 4 | 8.6 | N/A |
| Length of hospital stay (days) | 2.2 | 2 | 3.4 |
| Technical success (%) | 100 | 100 | N/A |
| Mean procedure length (minutes) | 50 | 54.2 | N/A |
| Yearly recurrence rate (%) | 13 | N/A | N/A |
| Factors associated with failure | High BMI, long duration, psych, pain medication users | Non-DM, long duration, non N/V, high GCSI | See text for G-POEM predictive score |

BMI, body mass index.

stimulator device, gastric perforation, and chronic pain. In the group of patients that underwent G-POEM, there was a shorter procedure time, lower incidence of new-onset acute abdominal pain, and lower incidence of adverse effects.⁴¹

G-POEM versus surgery

Surgical interventions for refractory gastroparesis include implantation of GES, Roux-en-Y gastric bypass, or subtotal gastrectomy. The intervention with the highest level of current evidence is GES. Surgical techniques that avoid or delay resections and bypasses are usually better tolerated by patients. G-POEM and laparoscopic pyloroplasty (LP) have a similar technique of dividing the pylorus, but G-POEM is less invasive than open or laparoscopic surgery. It is proposed that patients that undergo G-POEM compared to LP will have similar outcomes but without the perioperative morbidity.²¹

Pylorus division can be achieved reliably with G-POEM when compared to any surgical technique. Study results have shown improvements in symptoms and objective gastric emptying in both LP and G-POEM, suggesting that pylorus-targeted therapy is an effective technique. Both patient groups showed improvement in GES and

GCSI scores with no significant differences between the two groups. G-POEM is superior to LP when comparing metrics evaluating perioperative morbidity including operative time, estimated blood loss, and length of hospital stay.²¹

Both cohorts had one patient that required a surgery in the 30-day follow-up period. In the G-POEM cohort, one patient required a diagnostic laparoscopy for persistent abdominal pain, which was negative. In the LP cohort, one patient required placement of a jejunostomy tube shortly following the procedure. Overall, G-POEM had fewer complications, but the two procedures have different risks for complications, making it difficult to compare.²¹

G-POEM has less pain following the procedure as well as faster recovery when compared to LP. Faster recovery is evaluated based on length of hospital stay, which was shorter overall in G-POEM patients. One mortality was seen in the G-POEM cohort, and upon further evaluation was deemed to be an unrelated cardiac death. This was the only mortality in over 200 patients evaluated at the institution, establishing that G-POEM continues to be considered a safe treatment option. Treatment with G-POEM or LP does not indicate that a patient will not be able to

undergo the other treatment in the future if needed. Many patients in this study underwent G-POEM after failing LP and vice versa.²¹

In G-POEM, there is a lesser curve approach where the pyloric incision is 90° offset when compared to LP. For patients who fail other organ preserving interventions, neither LP and G-POEM are contraindications to future gastrectomy or bypass. Therefore, G-POEM and LP are considered first line, leaving more invasive treatments available as options further down the line. In addition, in G-POEM, there is no violation of the peritoneal space. This may have less risk of scarring and adhesions that may complicate future interventions. In conclusion, G-POEM has less perioperative morbidity than LP and should be considered a first-line option for refractory gastroparesis. Further studies are required to determine long-term efficacy for G-POEM compared to other surgical interventions.²¹

Endoflip

Endoflip, endoscopic functional luminal imaging probe, uses impedance planimetry to measure pressure and CSA of the pyloric sphincter, allowing for distensibility to be calculated. As of recently, Endoflip has been used mostly for lower esophageal sphincter assessment. A study done in France in 2018 was the first prospective trial of evaluating G-POEM with Endoflip.¹⁹ The procedures in this study had a median duration of 56.5 min with a good safety profile despite three perforations. The perforations, however, were done ‘voluntarily’ to ensure complete myotomy and effectiveness.²⁰

Improvements were assessed clinically and *via* scintigraph. Clinical improvement was defined as an improvement in the GCSI of at least 0.75, which was determined in the international validation study of the GCSI. There was a 90% rate of improvement, with a median of 65%. Many authors define clinical success as a reduction in GCSI of >1 because it appears to be more clinically relevant. With this criterion, the clinical success rate was 75%.²⁰

This study identified a distensibility threshold of 9.2 mm²/mmHg before the G-POEM procedure, predicting a clinical response with 100% specificity and 72.2% sensitivity. The PPV of this threshold was 100%, which indicates that patients with

distensibility below 9.2 mm²/mmHg reported clinical success. The NPV, however, was 28.5%. Therefore, Endoflip can potentially only identify patients that will respond to G-POEM, but not patients that will fail to have a response to G-POEM.²⁰

In another study done in 2020, the authors found that some post-G-POEM physiologic characteristics of the pylorus, measured with Endoflip, are associated with clinical success. CSA and distensibility index (DI) were shown to be increased after G-POEM, which would indicate an appropriate response of the pyloric sphincter. Increased CSA after G-POEM was the largest predictor of clinical success following G-POEM. Multiple past studies reported that CSA and DI increased while balloon pressure decreased, especially in diabetic patients, following G-POEM. This study suggests that pylorus CSA provides a high specificity for predicting 1-year clinical success. However, this finding is accompanied with a low sensitivity, suggesting that there might be a high false-negative rate clinically. In addition, the results of this study showed that the change in CSA and DI immediately after G-POEM was a better clinical success predictor than 3 months following G-POEM. This result may be attributed to variations in procedure and patient-specific factors between the initial encounter and 3-month follow-up.²⁴

Similar to the EndoFLIP is the newer esophageal dilator known as the EsoFLIP. The EsoFLIP can measure luminal diameters like EndoFLIP while also performing the dilation. Therefore, there is potential utility in relief of symptoms in achalasia and esophageal strictures. EsoFLIP can dilate over large diameters, 10–30 mm, with one balloon. In addition, there is avoidance of fluoroscopy and radiation.⁴²

In a study reported in 2021,⁴³ balloon dilation was done incrementally with a goal of 25 mm diameter. Maximal inflation was maintained for 2 min. Follow-up was done 2–3 weeks after the procedure and then also at 12 weeks. Clinical success was seen as an improvement in gastric emptying time and GCSI scores. Gastric emptying half-times, measured at a median of 21 days post-procedure, decreased from 211 to 179 min. In all patients that had gastric emptying half-times longer than 180 min, 41% had a decrease to less than 180 min. Initial GCSI scores were 2.78

before dilation. The GCSI scores decreased from 2.44 at the first follow-up appointment and then to 1.95 after 3 months of the procedure. At the 3-month follow-up visit, 53% of patients had a reduction in the mean GCSI score of greater than 0.5 points, which was deemed clinically significant. Symptoms of retching and vomiting did not show any statistical improvement. Abdominal pain as a symptom was not uniquely assessed. Pyloric distensibility increased from a median of 9 to 13 mm²/mmHg after the procedure. Diameter increased from 17 to 20 mm. No perforations or hospitalizations occurred, but there were lacerations following dilation in all patients except one.⁴⁴

Sham study

A recent study reported in 2022 is the only study available comparing G-POEM outcomes with a placebo. In this study, 71% of patients in the active arm had a significant treatment effect compared with 22% in the control group, which received upper endoscopic examination without pyloromyotomy. In addition, clinical success was achieved in 75% of patients in the control group after cross-over G-POEM 6 months later. G-POEM resulted in improvement in gastric emptying and increased pyloric distensibility.⁴⁵

In addition, two placebo-controlled trials did not show a clinical benefit of intrapyloric injection of botulinum toxin injection. In this study, patients with DG had a notable effect compared with postsurgical and idiopathic gastroparesis. The numerical difference between active and sham groups was much lower when comparing postsurgical and idiopathic gastroparesis patients.³⁸ One female patient with postsurgical gastroparesis did not have clinical success after G-POEM but underwent an additional G-POEM with excellent clinical success. This suggests that either the first G-POEM was not done effectively or a double myotomy might be required in some patients.⁴⁵

The largest subgroup of patients in this study was patients with DG with a predominance for type 1 diabetes. These patients had the best response to G-POEM which might suggest that this study enrolled patients with severe symptoms, predicting good clinical success after G-POEM. Treatment success was defined as a 50% reduction in symptoms from the baseline index. This threshold was set high to prevent confounders and make the results more clinically meaningful.⁴⁵

This study highlights the need for a standard definition of treatment success to be established so that studies can be better compared. There were 10 adverse effects documented, with only 3 being related to pyloromyotomy. Therefore, the adverse event rate was similar to that of other studies. This study had one case of moderate dumping syndrome and another facility had one report of refeeding syndrome. No patients in this study experienced new onset or worsening of duodenogastric reflux, which is a potentially severe adverse effect of G-POEM. Limitations of this study include follow-up of only 6 months, lower number of randomized patients, measurement of gastric emptying at a different time than primary endpoint, lack of investigation of pathophysiological parameters, and the use of one single endoscopist.⁴⁵

Redo G-POEM and same day discharge

As mentioned above, all three long-term outcome studies showed that each year, there were 13% or more patients with recurrence of gastroparesis; thus, management of those patients is challenging. One small study showed that redo G-POEM was feasible, safe, and had some efficacy.³¹

Also as mentioned above, G-POEM is a safe procedure; a recent study indicates that about 50% of patients can be discharged to home after G-POEM on the same day without admitting to hospital for observation.⁴⁶

Predictors of success

Identifying predictors of G-POEM success is important to select patients most likely to benefit from G-POEM. Factors, such as high BMI, long duration of gastroparesis, and psychiatric or narcotic medication use, are associated with poor outcomes. A recent international prospective trial showed baseline GCSI greater than 2.6 and 4-h gastric emptying greater than 20% are associated with good 1-year outcomes.²⁸

One study attempted to correlate regional gastric dysmotility patterns and G-POEM outcomes. This was based on the hypothesis that patients with antral retention should benefit from G-POEM therapy. However, on the contrary, patients with a higher retention index (the proximal-to-total gastric half-time emptying ratio,

suggestive of proximal retention of the stomach) responded better to G-POEM.⁴⁷

A recent study published online ahead of print⁴⁰ showed that endoscopic findings did not predict G-POEM response. The author examined endoscopic findings, such as bile in the stomach, lack of pylorospasm, tight pylorospasm, and very tight pylorospasm, which was not predictive of the G-POEM response.⁴⁸

Interstitial cells of Cajal

Treating gastroparesis can be difficult due to lack of understanding of its pathology. A proposed mechanism of gastroparesis is a loss of ICC. There are many types of ICC that exist and work toward proper gastrointestinal motility. Surgical specimen of resected stomach in a patient with refractory gastroparesis showed depletion of ICC in the myenteric plexus and intramuscular layer of the gastrointestinal tract.⁴⁹

ICC cells can be damaged by viral infection, potentially explaining transient or delayed gastric emptying that presents in post-infectious gastroparesis. The gastric muscular layer is difficult to obtain for biopsy, which has proven to be a challenge in identifying the role of ICC in gastroparesis. Methods for obtaining these biopsies are either invasive or indirect. G-POEM is a new and reliable procedure that could be used to allow a conduit for direct biopsy to analyze ICC quantity.⁵⁰

In a study done by us and reported in 2021, results showed that patients with a greater depletion of ICC had a poorer response to G-POEM.⁵⁰ It is difficult to say whether clinical response is related to the number of ICC or if the number of ICC determined greater severity of disease process and therefore lack of response to intervention. However, this finding is still valuable because it provides predictive value regarding response to G-POEM in symptomatic patients. In animal models, ICC depletion shows a consistent correlation with delayed gastric emptying in subjects with type 1 diabetes. Other studies with mice showed that those with type 2 diabetes have accelerated gastric emptying or decreased gastric emptying, depending on whether levels of ICCs are increased or decreased. In animals, loss of ICC and normal morphology maybe reversed. This varies in humans, due to a multitude of factors such as anatomic location in the stomach as well

as histological location. Anatomically, the location could be in the body, antrum, or pylorus and histologically, the location depends on outer longitudinal *versus* inner circular muscular layers. Although there is a variety of results on this topic, a correlation exists between depleted ICC and gastroparesis. Limitations of this study include a predominately female population, incomplete separation of longitudinal and circular muscle, and lack of a control group. The sample size was small due to G-POEM being a new concept at the time of the study. In this study, ICC were present in all but one antrum histology sites. Patients with higher numbers of ICC responded the best to G-POEM. Submucosal endoscopy provides a new method of direct biopsy for research of ICC and their relation to gastroparesis.⁴⁹ Large sample studies are needed to confirm the finding. The role of ICC in treatment for gastroparesis is not clear. It is difficult to compare patients with gastroparesis to a control group since it is unreasonable to do a gastric biopsy in a patient without symptoms of gastroparesis. More studies should be done to look at ICC cell populations in patients with gastroparesis.

Conclusion

Many studies have shown that the short-term (6 month to one year) clinical success rate of G-POEM is about 50–80%. Three long-term outcome studies indicate a durable efficacy at 4 years but with a significantly recurrence rate of 13% or higher. Predictors for clinical success of G-POEM is unknown at the present time. EndoFlip may have future utility in selecting patients that will respond to POEM by measuring the CSA of the pylorus and DI. G-POEM is a microinvasive procedure and is safe with experienced hands. Some patients can be safely discharged to home on the same day of the procedure. G-POEM may open a path for future research on the role of ICC in the pathogenesis of gastroparesis, since G-POEM makes the direct biopsy of the gastric muscle feasible through endoscopy.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors have consented for publication.

Author contribution(s)

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Shazia Rashid: Writing – review & editing.

Syed Musa Raza: Writing – review & editing.

James Morris: Writing – review & editing.

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Competing interests

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Availability of data and materials

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Supplemental material

Supplemental material for this article is available online.

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