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Original research

Gastric per-oral endoscopic myotomy (G-POEM) for refractory gastroparesis: results from an international prospective trial

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ABSTRACT

Objective Although gastric per-oral endoscopic myotomy (G-POEM) is considered a promising technique for the management of refractory gastroparesis, high-quality evidence is limited. We prospectively investigated the efficacy and safety of G-POEM in unselected patients with refractory gastroparesis.

Design In five tertiary centres, patients with symptomatic gastroparesis refractory to standard medical therapy and confirmed by impaired gastric emptying were included. The primary endpoint was clinical success, defined as at least one score decrease in Gastroparesis Cardinal Symptom Index (GCSI) with ≥25% decrease in two subscales, at 12 months. GCSI Score and subscales, adverse events (AEs) and 36-Item Short Form questionnaire of quality of life were evaluated at baseline and 1, 3, 6 and 12 months after G-POEM. Gastric emptying study was performed before and 3 months after the procedure.

Results Of 80 enrolled patients, 75 patients (94%) completed 12-month follow-up. Clinical success at 12 months was 56% (95% CI, 44.8 to 66.7). GCSI Score (including subscales) improved moderately after G-POEM ($p<0.05$). In a regression model, a baseline GCSI Score >2.6 (OR=3.23, p=0.04) and baseline gastric retention >20% at 4 hours (OR=3.65, p=0.03) were independent predictors of clinical success at 12 months, as was early response to G-POEM at 1 month after therapy (OR 8.75, $p<0.001$). Mild procedure-related AEs occurred in 5 (6%) patients.

Conclusion G-POEM is a safe procedure, but showed only modest overall effectiveness in the treatment of refractory gastroparesis. Further studies are required to identify the best candidates for G-POEM; unselective use of this procedure should be discouraged.

Trial registration number ClinicalTrials.gov Registry NCT02732821.

Significance of this study

What is already known on this subject?

- Gastroparesis is a morbid disorder that remains difficult to treat with limited therapeutic options.
- Gastric per-oral endoscopic myotomy (G-POEM) is a minimally invasive procedure that has shown promising results for the management of refractory gastroparesis.

What are the new findings?

- G-POEM was only modestly effective in patient with gastroparesis with a clinical success rate of 56% at 12 months.
- Serial assessment of gastroparesis symptoms showed that the response to G-POEM was durable throughout the course of the study.
- Baseline gastric retention >20% at 4 hours and symptom severity were independent predictors of clinical success 12 months after G-POEM.

How might it impact on clinical practice in the foreseeable future?

- The accurate mid-term clinical success and durability of outcome helps clinicians to better decide about performing G-POEM.
- Our findings of mid-term clinical success and durability of G-POEM may help physicians to choose the best therapeutic strategy for patients with refractory gastroparesis.
- G-POEM may be considered in patients with more severe baseline symptoms and pre G-POEM gastric retention.

INTRODUCTION

Gastroparesis is a morbid disorder, characterised by delayed gastric emptying in the absence of mechanical obstruction.[1] Over the past two decades, gastroparesis has been a growing concern in terms of prevalence, economic cost and its negative effect on quality of life.[2–4] Despite its high burden, gastroparesis remains a difficult-to-treat condition with limited treatment options. One large multicentre prospective study showed that only 28% of patients had clinical success at 48 weeks after receiving treatment according to the standard of care.[5] Impairment of fundic accommodation, antral contractility, pyloric relaxation and/or duodenal feedback may

contribute to delayed gastric emptying and clinical symptoms.[6 7] Treatment of gastroparesis remains challenging due to contribution of various pathophysiologic mechanisms to the disease. Diet modification and prokinetic medications are first-line therapies of gastroparesis. However, prokinetics are not tolerated well due to their significant side effects and have suboptimal efficacy.[8]

Pylorospasm, detected by manometry[9] and endoluminal impedance planimetry (EndoFLIP; Medtronic, Minneapolis, Minnesota),[10–12] has been shown to correlate with gastroparesis symptoms. Based on these findings, pyloric-directed interventional procedures such as botulinum toxin injection, transpyloric stent placement and pneumatic dilation of the pylorus have been developed.[13–16] Unfortunately, long-term efficacy of these interventions has not been confirmed in robust prospective studies.

Gastric per-oral endoscopic myotomy (G-POEM) was introduced by Khashab *et al*[17] in 2013 as a minimally invasive pyloric-directed procedure for the management of refractory gastroparesis. This was followed by several studies, mostly retrospective with short follow-up periods, which showed encouraging results.[18 19] Two meta-analyses reported pooled symptomatic improvement rates of 83.9% and 82% and adverse events (AEs) rate of 6.8% and 6.1%, respectively.[20 21] These results have contributed to our knowledge about efficacy and safety of G-POEM; however, the literature remains scarce, and prospective multicentre trials with mid-term to long-term follow-up are lacking.

In this international multicentre, prospective study, we aimed to assess clinical success of G-POEM for the management of refractory gastroparesis 12 months after the procedure. Secondary aims were to evaluate safety, change in quality of life and change in gastric retention over the course of the study.

METHODS

Study design

We designed an international multicentre, prospective study to evaluate the safety and efficacy of G-POEM and its effect on gastroparesis-related symptoms, quality of life and gastric emptying.

Patients

Patients with refractory gastroparesis referred for possible G-POEM at five participating centres were eligible for the study. Following a detailed description of the intended procedure, patients were invited to participate in the study if they were deemed eligible. Eligible participants were patients with refractory gastroparesis, aged 18 years or older. Refractory gastroparesis was defined as gastroparesis symptoms (nausea, vomiting, early satiety, belching, bloating and/or upper abdominal pain) in the absence of mechanical obstruction which are refractory to standard medical therapy (including diet, lifestyle modification and prokinetics) and confirmed by impaired gastric emptying. Baseline symptom severity was not an inclusion criterion. Exclusion criteria were previous surgery of the oesophagus or stomach which has resulted in a resection of the antrum and pylorus, known active gastro-oesophageal malignancy, prior surgical or laparoscopic pyloromyotomy, active opioid abuse, upper gastrointestinal (GI) bleeding conditions, use of anticoagulation therapy which could not be discontinued and pregnancy or expecting to become pregnant. Eligible patients provided written, informed consent before enrolment in the study.

G-POEM procedure and post procedure management

Procedures were performed by interventional endoscopists in the endoscopy unit under general anaesthesia. Details of the G-POEM procedure have been described previously.[22] In summary, intravenous antibiotics were administered before the procedure, and carbon dioxide insufflation was used throughout the procedure. G-POEM starts with creating a submucosal bleb 4–5 cm proximal to the pylorus along the greater curvature by injecting saline and 0.25% indigo carmine or methylene blue solution. A longitudinal 1.5 cm mucosal incision is made and the endoscope is introduced into the submucosal space. A tunnel is created and carefully extended by dissecting the submucosal fibres until the pyloric ring is identified. As the submucosal dissection is extended towards the pylorus, attention is paid to ensure the mucosal layer is not breached and the scope is correctly advancing towards the pylorus. A single myotomy is performed once the pyloric ring is identified from the most distal aspect of the pylorus with 2–3 cm extension proximally towards the antrum and entails full-thickness pyloromyotomy involving circular and oblique muscle bundles. Finally, the mucosal incision is closed using endoscopic clips (online supplemental video 1). On day 1 post procedure, an upper GI series was performed for all patients to rule out any leakage. In case of normal upper GI series, patients were started on a full liquid diet with transition to soft diet if tolerated. Subsequently, if patients tolerated the oral diet without vomiting, they were discharged with instructions to stay on soft diet for 10–14 days. The diet was subsequently advanced to a low residue diet as tolerated.

Assessments and outcome measures

At baseline and at 1, 3, 6 and 12 months, the Gastroparesis Cardinal Symptom Index (GCSI) Score, use of prokinetics, 36-Item Short Form (SF-36) quality of life questionnaire and AEs were recorded. Gastric emptying scintigraphy (GES) was performed at baseline and 3 months post G-POEM. Table 1 provides an overview of the plan of the study assessments. At baseline and each follow-up, the local site investigator contacted the participants and asked the items of GCSI and SF-36 questionnaire and recorded prokinetic use and any AEs.

GCSI, a patient-reported tool for assessment of severity of gastroparesis symptoms, includes three subscales of postprandial fullness/early satiety (four items), nausea/vomiting (three items) and bloating (two items). GCSI total score and each

Table 1 Study plan and schedule

	Baseline	During the procedure	1 month	3 months	6 months	12 months
GCSI Score	✓		✓	✓	✓	✓
Use of prokinetic medication	✓		✓	✓	✓	✓
SF-36 questionnaire of quality of life	✓		✓	✓	✓	✓
Adverse events	✓	✓	✓	✓	✓	✓
Gastric emptying study	✓			✓		

GCSI, Gastroparesis Cardinal Symptom Index; SF-36, 36-Item Short Form.

of the three subscales are 5-point Likert scales with 0=none, 1=mild, 2=moderate, 3=severe and 4=very severe.[23] Clinical success was defined as at least one score decrease in the total GCSI scoring system with more than a 25% decrease in at least two of the subscales as previously defined by Mekaroonkamol *et al*.[24] The primary endpoint was clinical success at 12 months after G-POEM.

Initially, when the study started at 2015, the primary endpoint was defined as GCSI Score below 2 at 12 months after G-POEM. However, as the knowledge of the field evolved, in January 2019, the primary endpoint was revised as defined above. The rate of patients with mean GCSI <2 has also been reported for comparison with the results of the modified primary endpoint.

Secondary endpoints of the study were clinical success at 1, 3 and 6 months, the change in average GCSI, GCSI subscales, prokinetic medication use and SF-36 quality of life score at 1, 3, 6 and 12 months and change in gastric retention at 3 months. SF-36 questionnaire was used to assess eight domains of quality of life including physical function, bodily pain, role-physical, general health, vitality, social function, role-emotional and mental health.[12] GES was performed before and 3 months after the procedure. The percentage of gastric retention was measured by scintigraphy after ingestion of low-fat, egg-white meal labelled with radioactive technetium.[13] Abnormal GES was defined as gastric retention greater than 10% at 4 hours after ingestion.[25] GES at 3 months was compared with preprocedure GES, and a reduction of at least 50% in gastric retention percentage at 4 hours was considered as GES improvement.

Safety of G-POEM was evaluated by the frequency and severity of the procedure-related AEs. Site principal investigators (PIs) recorded and rated severity, attribution and timing of AEs based on the American Society for Gastrointestinal Endoscopy lexicon's classification system.[26] During G-POEM, procedure details including duration of the procedure, length of incision, tunnel and myotomy and number of clips used alongside technical success (completion of the procedure using the assigned approach) and intraprocedure AEs were recorded by the site PIs.

Gastroparesis aetiology

Patients were classified into one of the three categories of postsurgical, diabetic and idiopathic gastroparesis. Patients with gastroparesis symptoms and delayed gastric emptying following a surgery with high probability of vagal nerve injury—eg, fundoplication, oesophagectomy, pancreatectomy, Roux-en-Y anastomosis and heart and lung transplant[27]—were classified in the postsurgical gastroparesis group. According to a general consensus, patients with diabetic gastropathy and delayed gastric emptying were classified in the diabetic gastroparesis group.[28] Patients with gastroparesis of unknown cause were classified into the idiopathic gastroparesis group. Patients with concomitant systemic, neurologic and psychiatric disorders as well as those on medications with a possible relationship (but without a clear causality association) to gastroparesis symptoms were reported in the idiopathic gastroparesis group.

Statistical analysis

We aimed at evaluating the outcomes of G-POEM in patients with refractory gastroparesis in a single arm prospective observational study. Simulation studies suggest that for observational studies with dichotomous outcomes, at least 60 participants would be needed to provide sufficiently tight CIs for the prospective evaluation of outcomes, which then can be used as the basis for future randomised controlled trials (RCTs).[29] Accordingly, we planned a sample size of 80 patients.

Descriptive statistics for patient demographics, baseline characteristics and procedural data are presented as mean±SD for normally distributed continuous variables, median and 25th–75th percentiles for ordinal variables or continuous variables with non-normal distribution and count and percentage for categorical variables.

The primary endpoint was reported as the percentage of patients with clinical success at 12 months. Multiple paired t-tests with Bonferroni correction were used to compare total and subscales of GCSI scores at follow-ups with the baseline values. Friedman test was performed for analysis the change of each domain of the SF-36 questionnaire from baseline and across the 12-month follow-up period, and Wilcoxon signed ranks test was used to compare 12-month values with the baseline. The rate of normalised GES was reported at 3 months and the 4-hour gastric retention at 3 months was compared with baseline using a paired t-test. Logistic regression model was used to determine baseline predictive parameters. Baseline variables with p value<0.02 were tested in a multivariable logistic regression model to identify independent baseline predictors of clinical success. Statistical analyses were performed using SPSS software (SPSS V.16.0). Two-sided p value<0.05 was considered as statistically significant.

Missing values of GCSI subscales were imputed using multiple imputation (MI) by fully conditional specification (FCS).[30] FCS MI uses functions conditionally on the information of a set of given variables to impute the missing values on a variable-by-variable basis. FCS was used since this method (unlike joint modelling, the major iterative alternative for doing MI) is flexible in using different regression models for each variable (eg, linear regression for continuous variables and logistic regression for categorical variables).[31] Moreover, simulation studies have shown that FCS MI generally provides unbiased estimates with appropriate coverage.[32 33]

The following variables were given to the model to impute missing values of GCSI subscales: available GCSI scores (including baseline), age, sex, body mass index (BMI), aetiology of gastroparesis, duration of gastroparesis and previous treatments. (132/1200 (11%) missing values for GCSI subscales at interim and 12-month follow-ups.) A total of 50 imputations were carried out with 100 iterations each. Missing values of average GCSI were calculated using the imputed GCSI subscale values. The missing values of quality of life, medication use and post G-POEM GES were not imputed.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS

Between November 2015 and November 2018, 80 patients at five centres fulfilled the study criteria. The number of patients recruited from each centre is displayed in online supplemental table 1. All 80 patients underwent successful G-POEM (100% technical success). Five patients did not complete the 12-month follow-up: four patients were lost to follow-up and one patient was not able to answer follow-up questions due to several hospital admissions for non-gastrointestinal medical issues. This resulted in 75 patients (94% of the sample population) who completed the 12-month follow-up with respect to the primary endpoint (figure 1). For the 80 participants, the mean age was 49.3±14.9

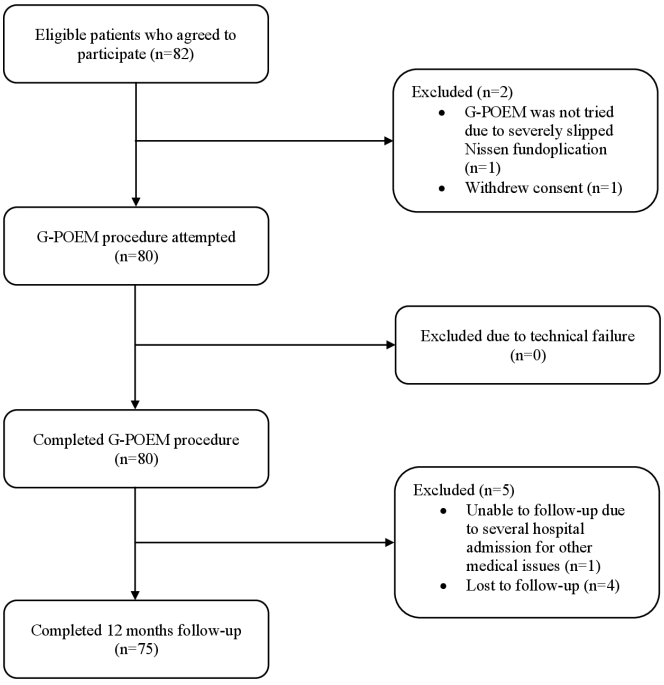

Figure 1 Enrolment flow diagram. G-POEM, gastric per-oral endoscopic myotomy.

(mean±SD) years and 57 (71.3%) were females. All patients had received prokinetic medications before enrolment. A total of 56 patients (70%) had previously been treated with intrapyloric botulinum toxin injection and/or transpyloric stent placement. Mean GCSI total score at baseline was 2.8±1.1 and mean gastric retention at 4 hours was 39%±22% (table 2). Online supplemental table 2 displays demographics and clinical characteristics in patients with complete 12-month follow-up versus those with missing 12-month follow-up. The most common aetiology of gastroparesis was idiopathic (n=33, 41.3%), followed by postsurgical (n=28, 35%) and diabetes (n=19, 23.8%). Further details related to each aetiology group are presented in online supplemental table 3.

Table 2 Demographics and patient characteristics*

	G-POEM (n=80)
Age—years	49.3±14.9
Sex—no. (%)	
Male	23 (28.7%)
Female	57 (71.3%)
BMI—kg/m^2	26.14±5.99
Previous treatment—no. (%)	
Prokinetic only	24 (30%)
Prokinetic and botulinum toxin injection	28 (35%)
Prokinetic and transpyloric stenting	16 (20%)
Prokinetic, botulinum toxin injection and transpyloric stenting	12 (15%)
Median disease duration (25th–75th percentiles)—months	36 (18–61)
Average GCSI Score at baseline	2.8±1.1
GCSI nausea/vomiting score at baseline	2.5±1.4
GCSI fullness/early satiety score at baseline	3.4±1.2
GCSI bloating subscale score at baseline	2.7±1.5
Gastric retention percent at 4 hours before the G-POEM	39±22
Median time difference between baseline GES and G-POEM (25th–75th percentiles)—months	16 (2.5–33.5)

*± values are means±SD.
BMI, body mass index; GCSI, Gastroparesis Cardinal Symptom Index; GES, gastric emptying scintigraphy; G-POEM, gastric per-oral endoscopic myotomy.

Table 3 G-POEM procedure details

Procedural data	Median (25th–75th percentiles)
Length of myotomy (cm)	2 (1.5–2)
Length of tunnel (cm)	5 (4–6)
Length of incision (cm)	2 (2–2)
Number of clips	5 (4–6)
Procedure time (min)	43 (34–56.5)
Length of hospital stay (days)	1 (1–1)

G-POEM, gastric per-oral endoscopic myotomy.

The G-POEM procedure was completed in 80 patients (100% technical success). Median (25th–75th percentiles) procedure time was 43 (34–56.5) min. All procedures were completed with the greater curvature approach (table 3).

Efficacy

Clinical success was achieved in 42 of 75 patients (56% (95% CI, 44.8 to 66.7)) at 12 months (the study's primary endpoint). Clinical success at the interim follow-ups were 57.5% (95% CI, 46.1 to 68.2) at 1 month, 61.5% (95% CI, 49.4 to 72.4) at 3 months and 60.3% (95% CI, 48 to 71.5) at 6 months after G-POEM.

Analyses of the total 80 participants using the imputed data obtained similar clinical success rates (57.3% (95% CI, 46.3 to 67.5) at 1 month and 56.3% (95% CI, 45.3 to 66.6) at 12 months).

At 12 months, GCSI Score <2 was observed in 51 of 75 patients (68%, 95% CI, 56.8 to 77.5) in the population with completed 12-month follow-up and in 53 of 80 (66.6%, 95% CI, 55.8 to 76) in the complete 80 patients, using the imputed data (table 4).

Clinical success rate at 12 months was generally consistent across gastroparesis subtypes: 59.3% (95% CI, 40.7 to 75.5) in the postsurgical group, 52.9% (95% CI, 31 to 73.8) in the diabetic group and 54.8% (95% CI, 37.7 to 70.8) in the idiopathic gastroparesis group (p=0.913). Clinical success rate and proportion of patients with GCSI Score <2 at 12 months are reported by baseline treatment groups and participating centres in online supplemental table 4.

Average GCSI decreased from 2.8±1.1 (mean±SD) at baseline to 1.6±1.1 at 1 month (1.2±1.3 reduction compared with baseline, p<0.001) and to 1.5±1.2 at 12 months (1.3±1.3 reduction compared with baseline, p<0.001) (figure 2A).

Nausea/vomiting score decreased from 2.5±1.4 at baseline to 1.2±1.2 at 1 month (1.2±1.3 reduction, p<0.001); however, it increased slightly over the course of the study and reached 1.4±1.4 at 12 months (1.02±1.6 reduction compared with baseline, p<0.001) (figure 2B). Postprandial fullness decreased by 1.3±1.7, from 3.4±1.2 at baseline to 2.1±1.5 at 1 month. The improvement continued and the score reached 1.8±1.4 at 12 months (1.5±1.5 reduction from baseline, p<0.001) (figure 2C). Likewise, bloating score decreased from 2.7±1.5 at baseline to 1.5±1.5 at 1 month (1.1±1.6 reduction from baseline, p<0.001) and further decreased to 1.3±1.5 at 12 months (1.3±1.7 reduction from baseline, p<0.001) (figure 2D).

Quality of life

A comparison of eight aspects of quality of life scores measured at baseline and 12 months, together with analysis of change in scores over the time course of the study, are shown in table 5.

Table 4 Clinical success rate and rate of patients with GCSI total score below two across the follow-up time points

	1 month		3 months		6 months		12 months	
	Number	Percent (95% CI)	Number	Percent (95% CI)	Number	Percent (95% CI)	Number	Percent (95% CI)
Clinical success* (available date)	42/73	57.5 (46.1 to 68.2)	40/65	61.5 (49.4 to 72.4)	38/63	60.3 (48 to 71.5)	42/75	56 (44.8 to 66.7)
Clinical success* (imputed data†)	45.8/80	57.3 (46.3 to 67.5)	46.8/80	58.5 (47.6 to 68.7)	49.7/80	62.1 (51.2 to 72)	45/80	56.3 (45.3 to 66.6)
Patients with GCSI <2‡ (available date)	49/73	67.1 (55.7 to 76.8)	40/65	61.5 (49.4 to 72.4)	38/63	60.3 (48 to 71.5)	51/75	68 (56.8 to 77.5)
Patients with GCSI <2‡ (imputed data†)	52.7/80	65.8 (55 to 75.3)	47.4/80	59.3 (48.3 to 69.4)	47/80	58.8 (47.8 to 68.9)	53.3/80	66.6 (55.8 to 76)

*Clinical success was defined as one score decrease in the five-point GCSI Score plus at least 25% decrease in two of the three GCSI subscales. The collected data showed that 25% decrease equals to 0.62 for nausea/vomiting, 0.84 for fullness/early satiety and 0.66 for bloating subscales.
†No. of patients with imputed observations: 7 (8.8%) at 1 month, 15 (18.8%) at 3 months, 17 (21.3%) at 6 months and 5 (6.3%) at 12 months.
‡The study's initial primary endpoint.
GCSI, Gastroparesis Cardinal Symptom Index.

There was a significant improvement in the majority of the quality of life aspects both at 12 months and over time. All components improved at 12 months except for physical functioning, role limitation due to physical health and bodily pain, which showed no significant change.

Gastric emptying study

Three months after G-POEM, GES was performed in 53 of the 80 patients (66%). Gastric retention at 4 hours was compared with the baseline values. Mean (±SE) gastric retention at 4 hours decreased significantly from 39±22% at baseline to 21±27% at 3 months, which resulted in GES improvement in 64.2% (34 of 53 cases). At 3 months, gastric retention normalised in 47.2% (25 of 53 cases) of the patients.

At 3 months, clinical success rate was 75.8% (25 of 33 cases) in patients with GES improvement compared with 38.9% (7 of 18 cases) in those who did not show GES improvement (p=0.015). Similarly, decrease of gastric retention at 4 hours and change in mean GCSI Score at 3 months were found to be moderately positively correlated (r=0.29, p=0.046).

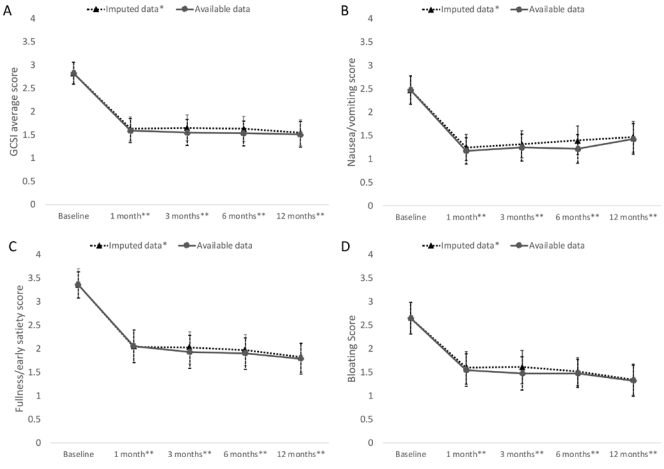

Figure 2 Change in GCSI Score after G-POEM over 12-month follow-up. Data presented as mean±95% CI over follow-ups in (A) average GCSI, (B) nausea/vomiting, (C) postprandial fullness/early satiety and (D) bloating scores. Analysis with paired t-test with Bonferroni correction was performed. *Number of imputed observations at each time point: 7 (9%) at 1 month, 15 (19%) at 3 months, 17 (21%) at 6 months and 5 (6%) at 12 months. **Indicates significant difference compared with baseline values (adjusted p value<0.0125). GCSI, Gastroparesis Cardinal Symptom Index; G-POEM, gastric per-oral endoscopic myotomy.

Safety

AEs were recorded and rated in all participants (n=80). No unanticipated AEs were reported. Five AEs (6.2%) were reported, all of them were rated as mild and were reported to be procedure related. AEs included symptomatic capnoperitoneum in three patients, all were successfully managed with needle decompression, mucosotomy in one patient, treated successfully by stent replacement and one thermal mucosal injury, treated with clipping.

Predictors of 12-month clinical success

Predictors of 12-month clinical success were evaluated using univariable logistic regression model. Baseline GCSI Score higher than 2.6, fullness/early satiety GCSI subscale, gastric retention of more than 20% at 4 hours before G-POEM and clinical success at 1 month were positively associated with 12-month clinical success (p<0.05) (table 6). Clinical success rate was constantly higher in patients who achieved 1-month clinical success compared with those with clinical failure at 1 month. At 12 months, clinical success rate in patients who achieved 1-month clinical success was 79%, compared with 30% in those with clinical failure at 1 month (p<0.001) (figure 3).

Multivariable analysis was performed for evaluation of preprocedure predicting factors. Our model showed that higher baseline GCSI Score higher than 2.6 (OR=3.23, p=0.04) and baseline gastric retention of more than 20% at 4 hours (OR=3.65, p=0.029) were independent predictors of clinical success at 12 months (table 7).

DISCUSSION

This international, multicentre, prospective study presents mid-term outcomes of G-POEM in patients with refractory gastroparesis. G-POEM resulted in a modest improvement of average GCSI and subscale scores which were sustained at 12 months post procedure. Almost half of the patients responded to G-POEM which is considerably lower than the rates reported by previous studies.[20 21] Our findings do not support regular use of G-POEM in the general patient population without identifying the optimal G-POEM candidates. Prospective data collection as part of formal institutional review board (IRB)-approved protocols is paramount to help researchers identify patients who have a high likelihood of response to G-POEM. Our data also showed that G-POEM resulted in a larger decrease of GCSI Score in patients with more severe symptoms and higher gastric retention at baseline. These criteria are important for future studies on G-POEM. Larger studies are needed to determine further selection criteria.

Table 5 Change of eight domains of quality of life after G-POEM measured with SF-36 questionnaire

	Pre G-POEM (n=80/80, 100%)	1 month (n=72/80, 90%)	3 months (n=64/80, 80%)	6 months (n=61/80, 76%)	12 months (n=72/80, 90%)	Difference between baseline and 12 months	Change over the course of the study	Change between baseline and 12 months
	Median (25th–75th percentiles)	Median (25th–75th percentiles)	Median (25th–75th percentiles)	Median (25th–75th percentiles)	Median (25th–75th percentiles)	Mean (95% CI)	P value*	P value†
Physical functioning	70 (35–91.25)	77.5 (50–98.75)	82.5 (45–95)	85 (60–97.5)	87.5 (56.25–100)	−14.8 (−21.6 to −8)	0.071	**<0.001**
Role limitation due to physical health	0 (0–75)	25 (0–100)	50 (0–100)	50 (0–100)	62.5 (0–100)	−14.5 (−25.3 to −3.7)	0.085	**0.008**
Role limitation due to emotional problems	66.7 (0–100)	100 (0–100)	100 (33.3–100)	100 (33.3–100)	100 (33.3–100)	−14.2 (−26.7 to −1.6)	**<0.001**	**0.034**
Vitality	40 (20–55)	50 (30–65)	55 (27.5–70)	50 (30–70)	50 (30–75)	−14 (−20.3 to −7.7)	**0.002**	**<0.001**
Mental health	64 (52–80)	68 (57–83)	68 (56–83)	72 (60–80)	72 (56–88)	−6.3 (−11.7 to −0.9)	**0.004**	**0.038**
Social functioning	50 (25–62.5)	56.25 (50–87.5)	62.5 (38.125–87.5)	75 (50–87.5)	75 (37.5–100)	−18.6 (−25.4 to −11.9)	**<0.001**	**<0.001**
Bodily pain	45 (22.5–67.5)	57.5 (32.5–80)	57.5 (33.125–85.625)	57.5 (43.125–87.5)	68.75 (45–90)	−19.8 (−27.2 to −12.3)	0.216	**<0.001**
General health	37.5 (25–55)	45 (30–61.25)	45 (30–65)	45 (27.5–65)	40 (25–65)	−5.3 (−10.4 to −0.3)	**0.004**	**0.021**

Bold indicates a statistically significant difference with a p-value less than 0.05.
*P values were determined from tests for trend using repeated-measures analysis whether the domains of quality of life improve over time (Friedman's test).
†P values were determined by comparing 12 months and baseline values (Wilcoxon signed ranks test).
G-POEM, gastric per-oral endoscopic myotomy; SF-36, 36-Item Short Form.

Table 6 Univariable analysis of predictors of G-POEM clinical success at 12 months

	OR	95% CI	P value
Baseline characteristics			
Age	1.02	(0.99 to 1.05)	0.293
Female versus male	1.41	(0.52 to 3.83)	0.501
BMI	0.96	(0.88 to 1.04)	0.272
Aetiology			
Idiopathic			
Diabetes*	0.93	(0.28 to 3.03)	0.9
Postsurgical*	1.2	(0.42 to 3.4)	0.735
Duration of gastroparesis	1	(0.99 to 1.02)	0.551
Upper abdominal pain before G-POEM	1.27	(0.95 to 1.69)	0.11
Baseline GCSI Score higher than 2.6†	3.84	(1.43 to 10.30)	**0.008**
Baseline average GCSI Score	1.94	(1.19 to 3.17)	**0.008**
Baseline nausea/vomiting score	1.38	(0.97 to 1.96)	0.077
Baseline Fullness/early satiety score	1.68	(1.12 to 2.54)	**0.013**
Baseline bloating score	1.41	(1.02 to 1.95)	**0.036**
GES results			
Gastric retention >20% at 4 hours before G-POEM	3.24	(1.07 to 9.78)	**0.037**
Early response to G-POEM			
Clinical success at 1 month	8.75	(2.9 to 26.38)	**<0.001**
Medication use after the G-POEM			
Prescribed opioids	0.4	(0.14 to 1.19)	0.099
Cannabinoid	0.59	(0.15 to 2.4)	0.46
Prokinetics at 12 months	0.5	(0.1 to 2.42)	0.389
Prokinetics at any of the follow-up time points	0.83	(0.29 to 2.37)	0.732

*Compared with idiopathic aetiology.
†2.6 cut-off point was identified using receiver operating characteristic curve and Youden's Index (details not presented).
BMI, body mass index; GCSI, Gastroparesis Cardinal Symptom Index; GES, gastric emptying study; G-POEM, gastric per-oral endoscopic myotomy.

In this study, the repeated evaluation of the GCSI Score allowed the assessment of mid-term durability of G-POEM. The participants were recruited from five tertiary referral centres and included all subtypes of gastroparesis and a wide range of age and BMI. The diversity of the participants increases external validity and thus generalisability of the results of this study.

Figure 3 Comparison of clinical success rate between the groups with clinical success and clinical failure at 1 month over study follow-up time points. Numbers are presented for the 73 patients (91%) with available 1-month clinical follow-up.

Table 7 Predictors of G-POEM clinical success at 12 months tested by multivariable logistic regression model

	OR	95% CI	P value
Baseline GCSI Score higher than 2.6	3.23	(1.06 to 9.9)	**0.04**
Gastric retention >20% at 4 hours before G-POEM	3.65	(1.14 to 11.66)	**0.029**

Note: the following variables were tested in the model: upper abdominal pain before G-POEM, baseline GCSI Score higher than 2.6, baseline nausea/vomiting, baseline Fullness/early satiety, baseline bloating score and gastric retention >20% at 4 hours before G-POEM.
GCSI, Gastroparesis Cardinal Symptom Index; G-POEM, gastric per-oral endoscopic myotomy.

Clinical success was achieved in 56% of the patients at 12 months, which is lower than the 73%–90% success rate reported by previous studies.[20 21 34] Most of the previously published studies, however, were retrospective in nature, with a small sample size, and some without a clearly defined eligibility criteria. Moreover, the discrepancy in success rate can partially be explained by lack of a standardised definition of clinical success. In a number of the previous studies, clinical success was defined as improvement of GCSI Score after G-POEM procedure.

In this study, we initially defined the clinical success primary endpoint as mean GCSI Score below 2. As primary retrospective reports on G-POEM became available in the literature, we modified the clinical success definition to a decrease of one average GCSI Score with >25% decrease in at least two GCSI subscales. The revised definition was first introduced by Mekaroonkamol *et al*[24] and was subsequently used by more studies on G-POEM.[35 36] Previous studies which reported minimal important difference (MID) of GCSI Score confirm that the definition of clinical success used in our study represents a clinically meaningful improvement of gastroparesis symptoms. MID represents the smallest improvement perceived by patients as beneficial. A randomised clinical trial, which used GCSI Score to test a novel ghrelin receptor agonist for diabetic gastroparesis, estimated that MID for total GCSI Score was 0.94.[37] Moreover, Revicki *et al*[38] estimated that the MID for a composite score of 4 items of the GCSI-Daily Diary (GCSI-DD) (nausea, bloating, excessive fullness and postprandial fullness), as a simpler validated alternative to the original GCSI-DD, was 0.73. These results suggest that the revised primary endpoint of this study, which includes one score decrease in the mean GCSI total score, represents a clinically significant improvement of gastroparesis symptoms.

In our sample population, clinical success rates based on the revised definition (decrease of one average GCSI Score plus 25% decrease in 2 GCSI subscales) were generally comparable to the rates of the patients with GCSI below 2 (the initial primary endpoint of the study) across the follow-up time points. Particularly, the clinical success rate at 12 months was moderately lower than the rate of the patients with GCSI below 2 at 12 months.

This study demonstrated that clinical improvement after the G-POEM procedure was sustained over the course of the study. This finding is in agreement with a retrospective study that included 30 cases and showed the clinical improvement after G-POEM was sustained 18 months after the procedure.[39] Our results showed that early response to G-POEM predicts the clinical success at 12 months after the G-POEM. These findings provide valuable information about the pattern of response to G-POEM over time and helps gastroenterologists with early decision-making regarding the next management plan after performing G-POEM.

Our multivariate model showed that the severity of clinical symptoms at baseline and pre G-POEM gastric retention >20% at 4 hours were independent predictors of clinical success. This finding suggests that G-POEM should be considered in patients with more severe symptoms along with significant retention on GES. Aetiology and duration of gastroparesis have been suggested by retrospective studies to be potential baseline predictors of clinical success. One study on refractory gastroparesis suggested that longer duration of gastroparesis predicted a worse outcome with G-POEM.[40] Other studies have suggested that patients with non-diabetic gastroparesis were more likely to have a favourable outcome after G-POEM.[41 42] However, conflicting data have demonstrated that diabetes predicts the improvement of pylorus characteristics following G-POEM.[43] Our findings did not show a significant association between clinical success and duration or aetiology of gastroparesis. In addition to clinical criteria, study of antral motility and pyloric spasm has been proposed to provide valuable data for optimal patient selection before G-POEM.[44]

Our results have important clinical and health service implications. Gastroparesis remains a clinically challenging syndrome with limited therapeutic options.[45] The prevalence of gastroparesis, emergency department visits and number of hospitalisations in the USA and the associated charges have increased during the past decade.[46 47] Our results show that G-POEM is a modestly effective, minimally invasive procedure that provides patients with a durable outcome in terms of symptom improvement and quality of life, suggesting that G-POEM may lead to reduction in healthcare cost and burden of refractory gastroparesis.

In this study, we used FCS MI method to impute the missing data regarding G-POEM efficacy. Simulation studies have shown that FCS MI generally provides unbiased estimates with appropriate coverage.[32 33] However, the main assumption is that data are missing at random.[31] Our results showed that the baseline clinical characteristics and clinical success rate at 1 month were comparable between the patients with complete and those with missing 12-month follow-up. Moreover, the rate of missing 12-month follow-up was only 6%. Although proportion of missing data is not the only factor that determines the influence of missing data, it has been suggested that statistical analysis is unlikely to be biased with less than 10% missingness.[48]

Our study has several limitations. First, this study lacks a placebo control group; hence, the estimation of the absolute clinical success rate and sham/placebo effect of G-POEM was not possible. Although G-POEM has not been compared with a placebo-controlled group, previous studies suggested the occurrence of a major placebo effect after other treatment options of gastroparesis, including pylorus-targeted interventions.[49–51] This study limitation should be addressed in sham-controlled randomised trials on G-POEM. Second, inability to sufficiently control important confounding variables could be a major threat to the study's internal validity. For example, the effect of prokinetic use might be a potential confounder which was not considered in the definition of the primary endpoint. Moreover, the outcome of the prior gastroparesis interventions was not recorded, whereas studies have suggested that response to prior pylorus directed intervention might predict the outcome of G-POEM.[52] Third, several patients were not available for repeat gastric emptying study at 3 months after the procedure; thus, no conclusion can be drawn about improvement or normalisation of gastric emptying of those patients. Lastly, gastric emptying was not evaluated at 12 months after the study, concurrently with the study's primary endpoint. Gastric emptying results at 12 months would provide more information to investigate the mid-term objective response to

treatment as well as the correlation between the objective and subjective outcomes.

In conclusion, G-POEM is safe and most AEs are mild. It is modestly effective for management of refractory gastroparesis after a follow-up period of 12 months. Severity of baseline clinical symptoms and significant (>20%) retention on preprocedural GES predicted the clinical success at 12 months. We suggest that G-POEM should continue to be performed as part of prospective IRB-approved studies to aid. These studies will be crucial to help further identify optimal candidates for G-POEM. Concurrently, we should strive to study different available methods to identify patients with pylorospasm. These include endoluminal functional luminal imaging probe (EndoFLIP; Crospon, Galway, Ireland), antroduodenal manometry, dynamic gastric MRI and scintigraphy.

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