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Original research

Endoscopic pyloromyotomy for the treatment of severe and refractory gastroparesis: a pilot, randomised, sham-controlled trial

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ABSTRACT

Objective Endoscopic pyloromyotomy (G-POEM) is a minimally invasive treatment option with promising uncontrolled outcome results in patients with gastroparesis.

Design In this prospective randomised trial, we compared G-POEM with a sham procedure in patients with severe gastroparesis. The primary outcome was the proportion of patients with treatment success (defined as a decrease in the Gastroparesis Cardinal Symptom Index (GCSI) by at least 50%) at 6 months. Patients randomised to the sham group with persistent symptoms were offered cross-over G-POEM.

Results The enrolment was stopped after the interim analysis by the Data and Safety Monitoring Board prior to reaching the planned sample of 86 patients. A total of 41 patients (17 diabetic, 13 postsurgical, 11 idiopathic; 46% male) were randomised (21 G-POEM, 20-sham). Treatment success rate was 71% (95% CI 50 to 86) after G-POEM versus 22% (8–47) after sham (p=0.005). Treatment success in patients with diabetic, postsurgical and idiopathic gastroparesis was 89% (95% CI 56 to 98), 50% (18–82) and 67% (30–90) after G-POEM; the corresponding rates in the sham group were 17% (3–57), 29% (7–67) and 20% (3–67).
Median gastric retention at 4 hours decreased from 22% (95% CI 17 to 31) to 12% (5–22) after G-POEM and did not change after sham: 26% (18–39) versus 24% (11–35). Twelve patients crossed over to G-POEM with 9 of them (75%) achieving treatment success.

Conclusion In severe gastroparesis, G-POEM is superior to a sham procedure for improving both symptoms and gastric emptying 6 months after the procedure. These results are not entirely conclusive in patients with idiopathic and postsurgical aetiologies.

Trial registration number NCT03356067; ClinicalTrials.gov.

Significance of this study

What is already known on this subject?

⇒ Gastroparesis (GP) is a gastric motility disorder with a complex pathophysiology, which is not completely understood.
⇒ Pylorospasm is believed to play a role in the pathophysiology of GP.
⇒ Endoscopic pyloromyotomy (G-POEM) is a new minimally invasive procedure with promising uncontrolled clinical results in patients with GP.

What are the new findings?

⇒ In this randomised and sham controlled trial that included 41 patients with severe GP, symptomatic improvement at 6 months was achieved in 71% of the patients after G-POEM compared with 22% after the sham procedure. Moreover, 75% of the patients achieved symptomatic improvement 6 months after cross-over G-POEM, which was offered to patients without treatment success after the sham procedure.
⇒ The trial was terminated early due to a significant result and given the risk of general anaesthesia in patients in the sham group.
⇒ Gastric emptying improved after G-POEM but did not change after the sham procedure.
⇒ The trial was not sufficiently powered to assess the effectiveness of G-POEM in the aetiology subgroups. Our results cannot be considered as fully conclusive in patients with idiopathic and postsurgical aetiologies.
⇒ The study design did not allow for the assessment of the relationship between symptom improvement at 6 months and changes in gastric emptying, as these two parameters were obtained at different time points after the procedure.

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

⇒ The spectrum of treatment methods that can be offered to patients with severe and refractory GP can be extended by G-POEM.

INTRODUCTION

Gastroparesis (GP) is a gastric motility disorder defined by the presence of upper abdominal symptoms and delayed gastric emptying in the absence of organic obstruction.[1 2] Two important aetiologies are diabetes mellitus and GP following oesophageal

or gastric surgery (postsurgical GP). In up to half of the patients with GP, no underlying aetiology can be identified, and these patients are referred to as having idiopathic GP. The symptoms include nausea, vomiting, early satiety, postprandial fullness, bloating and abdominal pain. In severe cases, GP may lead to weight loss, poor nutritional status and increased mortality.[1–4]

The pathophysiology of GP is multifactorial and incompletely understood. Delayed gastric emptying is a defining feature, and gastric hypomotility due to several underlying mechanisms is believed to play a major role as well.[1] However, the symptomatic benefit of prokinetic agents is often disappointing.[5 6] An inappropriately spastic pyloric muscle has also been suggested as another important pathophysiological factor.[1 7]

Because of this complex pathophysiology, effective treatment for GP is a clinical challenge, especially in patients with severe and refractory disease.[1 2 5 6 8] Treatment options consist of dietary measures, administration of prokinetics and antiemetics, compensation of underlying disease, nutritional support and other methods such as gastric electrical stimulation, but none of these options is supported by strong scientific evidence.[1 2 8] Pylorus-directed therapies (botulinum toxin injection, balloon dilation, surgical pyloroplasty) constitute another approach.[8 9] Their common aim is to decrease pyloric tone, which is thought to be increased in patients with GP.[7] However, these therapies have not been recognised as a standard mainly due to a lack of scientific evidence for their clinical efficacy.[9] Endoscopic pyloromyotomy (G-POEM) is a new pylorus-directed minimally invasive therapy, consisting of purely endoscopic myotomy. A multitude of non-randomised and non-controlled studies has shown promising clinical efficacy and high safety of G-POEM.[10–14] We performed a randomised trial comparing the clinical efficacy of G-POEM versus a sham procedure in patients with severe and refractory GP.

METHODS

Trial design

We performed a randomised and prospective trial at two European centres (Prague, Czech Republic; Trnava, Slovakia) comparing G-POEM with a sham procedure. All patients signed informed consent prior to enrolment. Patients were followed up for 6 months when treatment allocation was revealed and patients in the control group were offered cross-over G-POEM if they did not achieve treatment success. These patients were followed-up for another 6 months. Study design is summarised in online supplemental tables S4a and S4b and figure S1 in the Supplementary Appendix.

The trial was investigator initiated, was approved by the ethics committee at both centres and was performed in accordance with the provisions of the Declaration of Helsinki. No industry support was received except for a supply of Endoflip balloons by Medtronic.

An independent Data and Safety Monitoring Board (DSMB) surveilled the trial in terms of ethical consideration, patient's safety and data management. On-site data monitoring to ensure the proper conduct of the trial was provided by Axon CRO (online supplemental table S12). All coauthors have reviewed and approved the final manuscript.

Patients

Eligible were patients older than 18 years who suffered from severe (Gastroparesis Cardinal Symptom Index (GCSI) >2.3) and refractory (symptom duration>6 months) GP, which had to be confirmed by a gastric emptying study (GES; scintigraphy, abnormal gastric retention at 2 hours and/or 4 hours on a standardised sulphur colloid solid-phase GES, for details, see online supplemental table S7). Abnormal GES was defined as gastric retention greater than 60% at 2 hours and/or 10% at 4 hours after meal ingestion.[15] Main exclusion criteria were absence of a previous therapy trial with at least one prokinetic drug, major oesophageal or gastric surgery and previous pyloromyotomy or pyloroplasty. A complete list of inclusion/exclusion criteria is displayed in online supplemental tables S6a and S6b.

Randomisation

Patients were randomly assigned in a 1:1 ratio and the randomisation was stratified according to the performing centre, sex and aetiology of GP using randomly permuted six-patient blocks. A dedicated nurse performed the randomisation and a treatment allocation was revealed before the procedure just after induction into general anaesthesia.

Interventions

All patients were admitted to the hospital 1 day prior to the intervention and an upper endoscopy was performed to check for and eventually to clean the stomach from food residues. The patients randomised to the G-POEM group underwent G-POEM (under general anaesthesia) comprising four principal steps: (1) submucosal injection followed by mucosal incision 4–5 cm proximal to the pyloric channel, (2) creation of a submucosal tunnel towards a pyloric ring, (3) a complete myotomy 2–3 cm long, (4) closure of the incision with endoscopic suturing system or endoscopic clips.

The patients randomised to the control group underwent upper GI endoscopy under general anaesthesia, lasting at least 40 min. All procedures were performed by one experienced endoscopist with sufficient experience in submucosal endoscopy. Further details of the G-POEM are provided in the protocol (online supplemental file 1).

Before the procedure, the patients received parenteral antibiotics (or placebo in the control group), and after the procedure, the patients were administered a proton pump inhibitor (or placebo) intravenously on postoperative days 0 and 1 and then all patients received a proton pump inhibitor orally for at least 4 weeks.

We measured pyloric distensibility using the principle of impedance planimetry (Endoflip,[16 17]) before a procedure (G-POEM or sham) and two times after G-POEM. The first two measurements were performed under general anaesthesia with administration of opioids, the third measurement at 3 months was performed under sedation with midazolame. As Endoflip technology was not available when the trial started, measurements are available from patient No. 17 onwards. For details on this measurement, see online supplemental table S8 and figures S2a, S2b.

Trial follow-up

Clinical data were collected at follow-up visits at 3 and 6 months after G-POEM/sham procedure and 3 and 6 months after cross-over G-POEM. Patient-reported outcomes were assessed by means of follow-up appointments by dedicated trial personnel who were not aware of the treatment-group assignments. Objective evaluation by means of endoscopy, GES and Endoflip measurement was performed at 3 months after G-POEM/sham procedure and at 3 months after cross-over G-POEM. Online supplemental tables S4a and S4b and figure S1 provide an overview of the plan of the study assessment. We are further following

the patients to assess both clinical and objective parameters at 12, 24 and 36 months.

No medication was forbidden during the trial and patients were allowed to take prokinetics, antiemetics, antidepressants or other treatments on as needed basis. However, the prokinetics (and anticholinergics) had to be withdrawn at least 3 days before the GES. Pylorus-directed interventions were not allowed during the follow-up.

Primary and secondary outcomes

The primary outcome was the proportion of patients with treatment success at 6 months after the procedure in the intention to treat (ITT) cohort. Treatment success was defined as a decrease of at least 50% in the total GCSI (online supplemental table S5 in the Supplementary Appendix).[18 19]

The primary (null) hypothesis was that G-POEM leads to treatment success in the same proportion of patients as the sham procedure.

Secondary clinical outcomes included proportion of patients with treatment success at 3 months after G-POEM/sham, at 3 and 6 months after cross-over G-POEM, change in GCSI and PAGI-SYM score (online supplemental table S9)[20] and Quality of Life evolution assessed by using the validated PAGI—QoL questionnaire (online supplemental table S10).[21 22]

Prespecified objective outcomes included the change in gastric emptying after G-POEM/sham procedure/cross-over G-POEM and changes in pyloric distensibility and cross-sectional area. Further secondary endpoints included analysis of adverse events and procedure details.

The statistical analysis plan was described in the protocol and specified that clinically relevant exploratory subgroup analyses would be performed. Exploratory subgroups were defined according to aetiology of GP (diabetic, postsurgical, idiopathic).

Statistical analysis

The sample size calculation was based on the conservative estimation that the expected treatment success of G-POEM would be 50% of treated patients compared with 20% in the sham group at a significance level of 0.05 and a study power of 0.8. We planned to randomise 86 patients accounting for a 15% drop off. After the first interim analysis (performed, in accordance with the protocol after 40% (n=34) patients completed 6 months follow-up), the DSMB recommended to stop further enrolment as the analysis showed a highly significant result (p=0.003) in favour of the active treatment arm. The Board considered it ethically controversial to complete the originally planned number of enrolled patients given the risks of general anaesthesia in patients in the control group.

Analyses of the treatment success (main outcome), GCSI, PAGI-SYM, PAGI-QoL scores and GES were performed on the ITT population with the values missing for some of the 41 patients imputed using multiple imputation.[23] At most three values (7%) were missing for any of the variables in the imputation model. The 6-month GCSI value defining the treatment success was imputed in one patient (sham group). A sensitivity analysis was performed for the main outcome using the per-protocol population (PP). Analyses of the GCSI subscores and Endoflip measurements were analysed on available data basis.

The difference in treatment success between the G-POEM and sham groups was assessed using a logistic regression model, which resulted in the only p value presented in this report evaluating the only confirmatory hypothesis. All the remaining results are presented as point estimates (medians, means, HRs) with 95% CIs. We adopted this approach to provide more information and to prevent inadequate interpretations of p values due to the multiple testing. The reader can still identify statistically significant results as those having CIs entirely below or above zero. The CIs are presented without a correction for multiple testing.

CIs for the proportions of treatment success were calculated using the Wilson method and combined with multiple imputation according to Lott and Reiter.[24] The CIs for continuous variables were constructed by smoothed bootstrapping. For a detailed description of statistical analysis, see online supplemental table S11 in the Supplementary Appendix.

The statistical analyses were performed using R V.4.1.2 (packages tidyr 1.1.4, mice 3.13.0, Hmisc 4.6.0, ggpubr 0.4.0, ggplot 2 3.3.5).

Patient and public involvement

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

RESULTS

Patients

Between November 2017 and February 2021, a total of 41 patients were randomised (table 1, figure 1) and these patients represent the ITT cohort. Forty patients underwent the assigned procedure (21 G-POEM and 19 sham) while 1 male patient in the control group withdrew consent. One G-POEM could not be completed due to severe submucosal fibrosis. The per-protocol population (PP) comprised 39 patients (20 G-POEM, 19 sham procedure). Fifteen patients, who were originally randomised to the control group, were offered cross-over G-POEM, and 12 of them agreed to undergo it. All these patients received the procedure and completed the 6-month follow-up. Online supplemental table S12 in the Supplementary Appendix shows the distribution of patients between the two centres. Demographic data, symptom scores and Gastrointestinal Quality of Live scores at baseline were similar in both treatment groups (table 1). Procedural data are provided in online supplemental table S18. Surgeries on patients with postsurgical GP included fundoplication or refundoplication (n=12) and laparoscopic Heller myotomy (n=1).

Treatment success

In the intention-to-treat population, 15 of 21 patients (71%, 95% CI 50% to 86%) in the active treatment group and 4 of 20 patients (22%, 95% CI 8% to 47%, one patient imputed) in the control group had treatment success at the 6-month follow-up (the primary endpoint, figure 2, online supplemental table S19). In the per-protocol population (sensitivity analysis), the treatment success was achieved in 14 of 20 patients (70%, 95% CI 48% to 85%) in the G-POEM group and 4 of 19 patients (21%, 95% CI 9% to 43%) in the control group (figures 2 and 3 and online supplemental table S19). Three months after the assigned intervention, treatment success was present in 57% (95% CI 36% to 76%) in the G-POEM group and 22% (95% CI 8% to 47%) in the control group (online supplemental table S19 and figures S4 and S12).

Nine out of 12 patients (75%, 95% CI 47% to 91%) achieved treatment success 6 months after cross-over G-POEM (figure 2, online supplemental table S19).

In an analysis of treatment success with a logistic regression model, the OR for success at 6 months in the G-POEM group, as

Table 1 Demographic and clinical characteristics of the patients at baseline

Characteristic	G-POEM arm	Control (sham) arm
Number of patients	21	20
Sex—number (%)		
Female	11 (52.4)	11 (55.0)
Male	10 (47.6)	9 (45.0)
Age—median (Q1–Q3) (years)	43 (30 – 51)	51 (45 – 56)
BMI – median (Q1–Q3)(kg/m^2)	22 (19 – 28)	26 (21 – 28)
Aetiology—number (%)		
Diabetic; (diabetes type I/diabetes type II, number)	9 (42.9); (8/1)	8 (40.0); (6/2)
Post-surgical	6 (28.6)	7 (35.0)
Idiopathic	6 (28.6)	5 (25.0)
Previous therapy—number (%)		
Metoclopramide	12 (57.1)	10 (50.0)
Itopride	11 (52.4)	10 (50.0)
Domperidone	9 (42.9)	7 (35.0)
Other prokinetics	3 (14.3)	2 (10.0)
Enteral feeding via nasojejunal/nasogastric tube	3 (14.3)	1 (5.0)
Recurrent hospitalisation for gastroparesis-related symptom	8 (38.1)	7 (35.0)
Baseline GCSI score—median (Q1–Q3)*	3.5 (3.2–3.7)	3.2 (2.6–3.4)
Baseline PAGI-QOL score—median (Q1–Q3)†	2.1 (1.7–2.7)	2.5 (1.4–2.8)
Baseline 4 hours GES retention—median (Q1–Q3)(%)‡	22 (17–32)	26 (16–42)
Pre-procedure DI 40 mL—median (Q1–Q3)(mm^2/mm Hg)§	5.8 (4.8–9.8)	5.6 (3.5–6.2)

Q1–Q3—the first and the third quartile (representing the middle half of the observed values), the difference between Q3 and Q1 is the inter-quartile range.
*GCSI is a validated score assessing symptoms severity in patients with gastroparesis, consisting of nine items (symptoms) and three subscales (nausea/vomiting subscale, postprandial fullness/early satiety subscale and the bloating subscale). Each item can be graded from 0 (no symptom) to 5 (maximally severe symptoms). The total GCSI is calculated as the average of all three subscale averages. GCSI value ranges from 0 (no symptoms) to 5 (maximally severe symptomatology). The index evaluates symptoms during the last 14 days. Only patients with GSCI > 2.3 (indicating severe disease) were eligible for enrolment.
†PAGI-QOL score—a validated QoL questionnaire measures quality of life outcomes in patients with upper gastrointestinal disorders. It contains 30 items with five subscales (daily activities, clothing, diet/food habits, relationship, psychological well-being and distress). A total score is calculated by averaging subscales scores, its value ranges from 0 (perfect QoL) to 5 (worse QoL).
‡GES—is a validated method to demonstrate delayed gastric emptying in patients with gastroparesis. In this trial, all GES were performed according to a standardised method for measuring gastric emptying by scintigraphy; a low-fat, egg-white meal with imaging at 0, 1, 2 and 4 hours after meal ingestion was used for each patient. Only patients with a retention of Tc-99m > 60% at 2 hours and/or≥10% at 4 hours on a standardised sulphur colloid solid phase were eligible for enrolment.
§DI—pyloric distensibility is one among several parameters obtained from measurement of pyloric distensibility by using impendance planimetry principle (Endoflip). Values below 10 mm^2/mm Hg are thought to demonstrate a pylorospasm. In this trial, not all patients underwent Endoflip measurement as the method was not available when the trial started.
DI, Distensibility Index; GCSI, Gastroparesis Cardinal Symptom Index; GES, gastric emptying study; G-POEM, endoscopic pyloromyotomy; PAGI-QOL, Patient Assessment of Upper Gastrointestinal Disorders-Quality of Life.

compared with the control group, was 9.0 (95% CI 2.0 to 40.2, p=0.005) (table 2).

In patients with diabetic GP, the treatment success in the G-POEM group at 6 months was 89% (95% CI 56% to 98%, eight of nine patients), in postsurgical GP 50% (95% CI 18% to 82%, three of six patients) and in idiopathic GP 67% (95% CI 30% to 90%, four of six patients). The corresponding rates of treatment success in the sham group were 17% (95% CI 3% to 57%, one of seven plus one patient imputed), 29% (95% CI 7% to 67%, two of seven patients) and 20% (95% CI 3% to 67%, one of five patients) (figure 2, online supplemental table S19).

Exploratory analyses suggest that male gender, gastric retention at 4 hours below 20% and post G-POEM pyloric distensibility > 13 mm^2/mm Hg at 40 mL may predict a treatment success (table 2).

Secondary outcomes—symptoms and QoL

The median GCSI decreased in the G-POEM group from a baseline value of 3.5 (95% CI 3.2 to 3.7) to 1.4 (95% CI 0.9 to 1.9) at 3 months and 1.1 (95% CI 0.5 to 1.5) at 6 months postintervention, while in the sham group, it decreased from 3.2 (95% CI 2.8 to 3.4) to 2.5 (95% CI 1.9 to 3.1) at 3 months and 2.5 (95% CI 1.9 to 3.2) at 6 months (figure 3). The median reduction from baseline to 6 months was 2.4 (95% CI 2.0 to 2.8) in the active arm and 0.7 (95% CI 0.0 to 1.2) in the sham group (online supplemental table S20). Evolution of GCSI subscores is displayed in online supplemental table S21 and figures S5 and S6.

After cross-over G-POEM, GCSI significantly decreased from 2.8 (95% CI 2.5 to 3.7) to 1.0 (95% CI 0.6 to 1.7), the reduction from baseline was 2.1 (95% CI 1.3 to 2.6) (figure 3, online supplemental table S20, figures S5 and S6). Gastrointestinal Quality of Life Index score decreased from 2.1 (95% CI 1.7 to 2.5) to 0.8 (95% CI 0.6 to 1.5) showing a significant median reduction by 1.1 (95% CI 0.1 to 1.6) in the G-POEM group. In the sham group, the score decreased from 2.5 (95% CI 1.5 to 2.9) to 1.7 (95% CI 1.2 to 2.4) with a median reduction by 0.4 (95% CI −0.1 to 0.8). After cross-over G-POEM, the score decreased from 2.2 (95% CI 1.3 to 3.3) to 1.6 (95% CI 0.7 to 2.3) with the median reduction by 0.3 (95% CI 0.1 to 1.6) (online supplemental table S20, figure S8).

Secondary outcomes—objective parameters

Gastric retention at 4 hours decreased significantly after G-POEM but did not change after the sham procedure. Furthermore, gastric retention significantly decreased after the cross-over procedure. There was no correlation between GCSI and gastric retention at 3 months (r=0.15 (95% CI −0.18 to 0.42)). Detailed results on gastric emptying are shown at figure 4, online supplemental figures S9, S10, S12 and table S20.

Distensibility index at 40 mL (mm^2/mm Hg) increased from a baseline value of 7.6 (95% CI 6.0 to 9.3) to 12.7 (95% CI 11.4 to 14.3) after the procedure and to 13.1 (95% CI 11.3 to 15.7) at 3 months. The corresponding values for cross-sectional area (CSA, mm^2, 40 mL) were 144 (95% CI 125 to 165), 199 (95% CI 177 to 219) and 206 (95% CI 185 to 234). Detailed analysis of Endoflip measurements is provided in online supplemental table S22 and figure S11.

Safety

Ten serious adverse events (SAEs) occurred, 7 after G-POEM (five in the G-POEM group, two after cross-over G-POEM) and 3 in the sham group. All three SAEs in the sham group were not related to the procedure but rather to GP itself or to a newly diagnosed achalasia (online supplemental tables S15, S16).

Three SAEs were related to the G-POEM procedure (9% of all G-POEMs performed). One patient developed abdominal pain 1 day after G-POEM and was diagnosed with a gastric ulcer

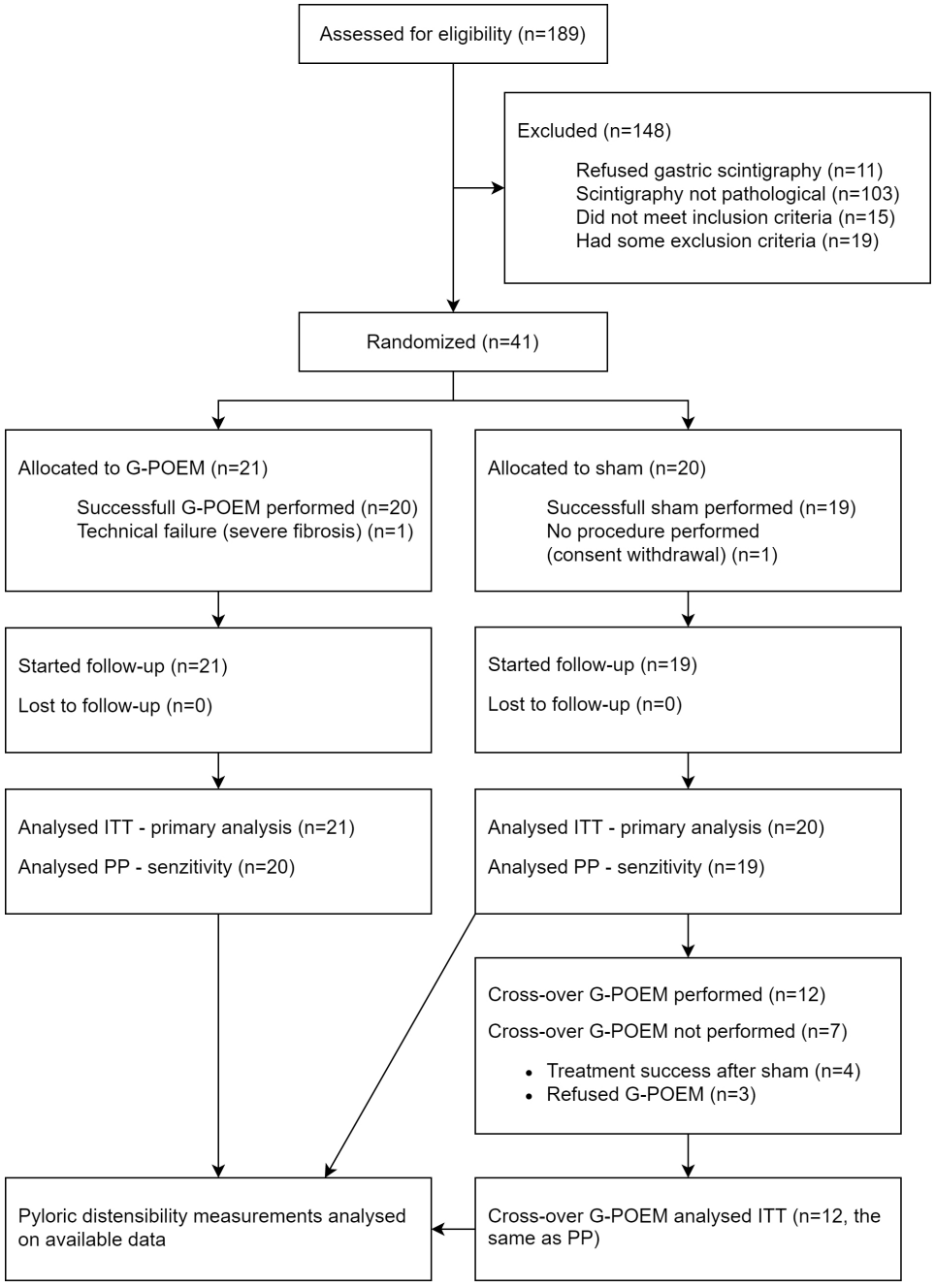

Figure 1 Flowchart demonstrating screening, enrolment, randomisation, follow-up and cross-over procedure with the subsequent follow-up. Eligible patients from the two centres were randomly assigned to either G-POEM or the sham procedure consisting of endoscopic examination under general anaesthesia. The length of the follow-up was 6 months when the treatment allocation was revealed. A total of 12 patients, who did not have treatment success after the sham procedure and agreed with a cross-over endoscopic pyloromyotomy (G-POEM), underwent the procedure and were followed up for another 6 months. The intention to treat (ITT) analysis comprises 41 patients, the per protocol (PP) analysis 39 patients.

near the pylorus. Conservative management was successful. Another patient had a mucosal injury during the G-POEM at the level of myotomy and was kept longer in the hospital as a precautionary measure. The third patient developed moderate dumping syndrome 3 months after the cross-over G-POEM with a need for hospitalisation, resulting in a complete resolution (online supplemental tables S15 and S16).

DISCUSSION

To our knowledge, this is the first prospective trial to compare the clinical effectiveness of G-POEM with a sham procedure in patients suffering from severe and refractory GP. Six months after the procedure, a significant treatment effect was achieved in 71% of patients in the active arm compared with 22% in the control group. Furthermore, treatment success was achieved in 75% of patients after cross-over G-POEM. G-POEM was associated with both improved gastric emptying and increased pyloric distensibility.

The two main mechanisms responsible for GP are believed to be postprandial gastric hypomotility and an abnormal control of pyloric muscle contractility resulting in pylorospasm.[1–3 7] Current treatment of GP is comprised of symptomatic measures

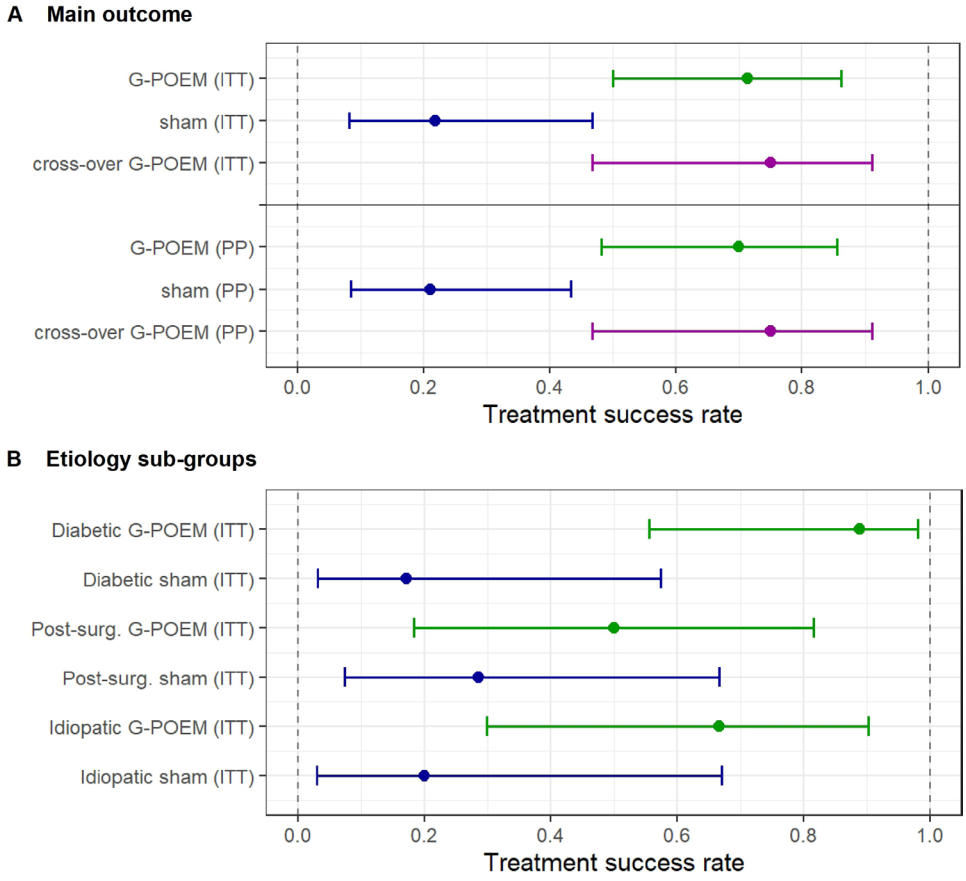

Figure 2 Treatment success at 6 months after the assigned procedure (main outcome), after the crossover G-POEM (A) and treatment success in sub-groups by aetiology of gastroparesis (B). The plot shows rates of treatment success with 95% CIs, where the clinical success is defined as reduction of the total Gastroparesis Cardinal Symptom Index (GCSI) score by at least 50% from the baseline. For the cross-over endoscopic pyloromyotomy (G-POEM), GCSI at 6 months after the sham procedure was considered as baseline. The results analysed on the intention to treat (ITT) population (N=41, N-Di-G-POEM=9, N-Di-Sham=8, N-PS-G-POEM=6, N-PS-Sham=7, N-Id-G-POEM=6, N-Id-Sham=5, 1 GCSI value (2 %) imputed in diabetic GP patient in the sham group) are supplemented by the main outcome analysis on the per protocol (PP) population (N=39).

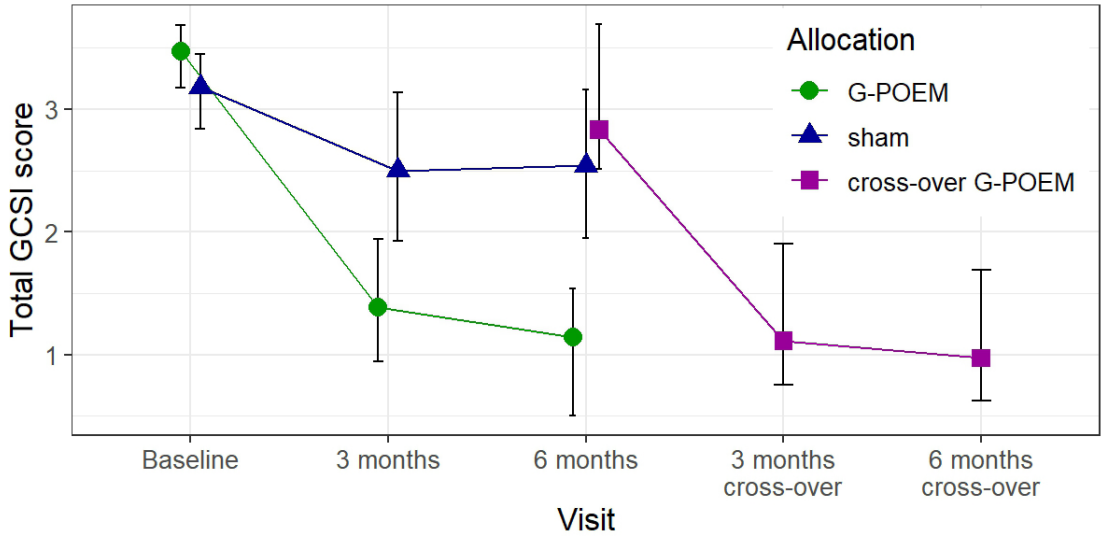

Figure 3 Evolution of the Gastroparesis Cardinal Symptom Index (GCSI) total score. Point estimates of medians with 95% CIs calculated on the intention to treat (ITT) population are shown for patients after the endoscopic pyloromyotomy (G-POEM) procedure (green circles, N=21), sham procedure (blue triangles, N=20, imputed 1 value (5 %) for 3 months and 1 value (5 %) for 6 months), and cross-over G-POEM procedure (purple squares, N=12). For the cross-over G-POEM group, the value at 6 months reflects only the data for the patients in this group (who subsequently underwent the cross-over G-POEM procedure). The GCSI score may range from 0 (no symptoms) to 5 (maximally severe symptoms).

Table 2 Primary treatment success comparison G-POEM versus sham at 6 months and predictors of treatment success at 6 months

Variable	OR*	95% CI for OR*	P value
Allocation G-POEM	9.0	2.0 to 40.2	0.005
Gender male	4.0	1.0 to 15.8	
Age >47 years	0.69	0.19 to 2.52	
Baseline GCSI >2.6	2.6	0.4 to 16.4	
Baseline GES 4 hours >20 %	0.24	0.06 to 0.93	
Baseline distensibility (DI) >8 mm^2/mm Hg†	3.6	0.5 to 33.6	
Post G-POEM distensibility (DI) >13 mm^2/mm Hg‡	6.0	0.66 to 136.8	

Each variable was tested as a predictor of treatment success in a separate logistic regression model. Only one p value for the main outcome is presented. The analyses of distensibility were performed on available data with N=19 for baseline distensibility and N=16 for post G-POEM distensibility. The remaining analyses used the ITT population with N=41, one treatment success value was imputed and there were no missing data in the predictor variables.
*Single parameter statistical significance can be judged by the CI for OR lying entirely below (reduced chance of treatment success) or above (increased chance for treatment success) the value of 1.
†Includes sham patients who did not undergo cross-over G-POEM, data for 40 mL filling.
‡Primary G-POEM and cross-over G-POEM combined, data for 40 mL filling.
DI, Distensibility Index (Endoflip measurement); GCSI, Gastroparesis Cardinal Symptom Index; G-POEM, endoscopic pyloromyotomy; ITT, intention to treat.

(dietary adjustments, antiemetics, nutritional support) as well as causal treatments targeting the proven or assumed pathophysiological mechanisms (prokinetic drugs, gastric electrical stimulation, pylorus-directed therapies).[1–3 5 6 8 9] Despite the existence of several options, treatment of GP is often partially effective or ineffective.[4–6 8 9 25]

Pylorospasm is believed to be an important pathophysiological factor, which was first demonstrated in 1986 by finding an increase of baseline pyloric tone in 60% of symptomatic diabetic patients.[7] Further evidence came from experimental studies, showing, for example, an insulin-sensitive reversible loss of neuronal nitric oxide synthase responsible for relaxation of the pylorus in diabetic mice.[26] To date, the main evidence has been brought by several studies showing some clinical effectiveness of pylorus-directed therapies, including G-POEM.[10–14 27–29] G-POEM showed short and mid-term clinical efficacy in 56%–81% of patients and improved gastric emptying in several uncontrolled and non-randomised studies.[10–14 30]

Not all data corroborate the hypothesis that pylorospasm plays the dominant pathophysiologic role in patients with GP. For example, a substantial number of patients do not respond to G-POEM, and partial efficacy has been reported for several treatments that do not influence pyloric tone.[1–3 8 31] In addition, two placebo-controlled trials did not show a benefit of intrapyloric injection of botulinum toxin injection.[32 33]

G-POEM should be indicated in patients with proven pylorospasm. The key question, however, of how to select these candidates remains. Unfortunately, no specific GP symptom pattern or aspect is associated with pylorospasm. Furthermore, it is not known whether different aetiologies of GP are associated with a differential response to pylorus-directed treatment. Based on previous[28] as well as the current study, measurement of pyloric distensibility by impedance planimetry may be a promising tool for patient selection. However, to date, normal values have not yet been defined and the protocol of measurement is not well standardised.

Our trial demonstrated a favourable effect of G-POEM in unselected patients with GP. This was most clearly the case in patients with diabetic GP while in the smaller subgroups of patients with postsurgical and idiopathic GP, the differences between active and sham treatment were numerically lower. Of note, one female patient in the postsurgical group without treatment success after initial G-POEM underwent redo-G-POEM with an excellent effect. It may signify that either the first G-POEM was not done well, or, that a double myotomy may be required in some patients as suggested by one retrospective study.[34] It is noteworthy that had this postsurgical patient had treatment success with the initial G-POEM, the rate of treatment success in the postsurgical group would be 67% (95% CI 30 to 90).

Another prospective trial reported rather modest (56%) clinical effectiveness of G-POEM 12 months after the procedure.[12] There may be several explanations for this difference.

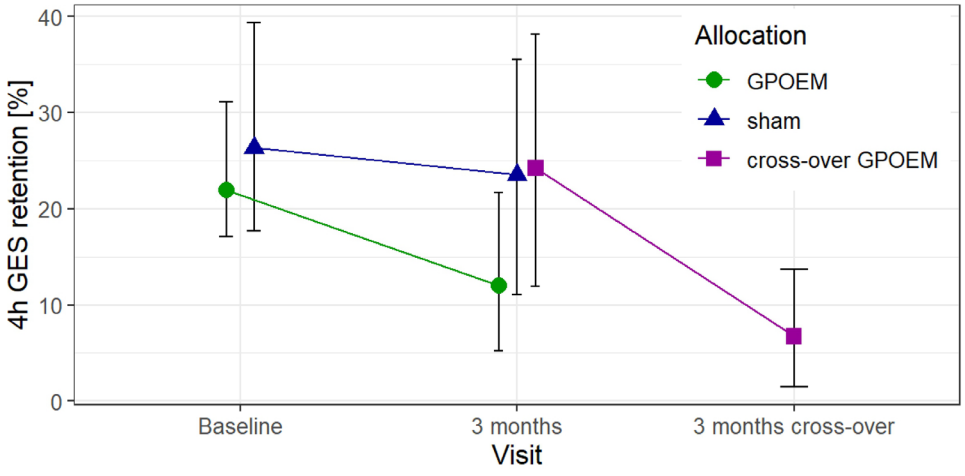

Figure 4 Evolution of gastric retention at 4 hours after meal ingestion on a standardised sulphur colloid solid-phase gastric emptying study (scintigraphy). Point estimates of medians with 95% CIs are shown for patients after the G-POEM procedure (green circles, N=21, imputed 2 values (10 %) for 3 months), sham procedure (blue triangles, N=20, imputed 1 value (5 %) for 3 months), and cross-over GPOEM procedure (purple squares, N=12). For the cross-over G-POEM group, the value at 3 months reflects only the data for the patients in this group (who subsequently underwent the cross-over G-POEM procedure). GES, gastric emptying study; G-POEM, endoscopic pyloromyotomy.

For example, in our trial, the largest subgroup of patients had diabetic GP (with a predominance of type I diabetes) and this aetiology responded best to G-POEM. In the study by Vosoughi *et al*, diabetic GP accounted for the smallest subgroup of patients (with a predominance of type II). Or, we enrolled patients with severe symptoms, the presence of which may predict good clinical effect of G-POEM.

Our primary endpoint was treatment success defined as a 50% reduction from the baseline symptom index. By contrast, in some previous studies, treatment success was defined as a decrease of the symptom score of at least one point.[10 12 14 30] However, this is a relatively low threshold, which may well be susceptible to spontaneous improvement and placebo effects. The choice of a 50% reduction sets a higher threshold, which is less susceptible to these confounders[35] and is clinically meaningful. Nevertheless, if we had defined our treatment success similarly to other studies, the difference between active treatment and control groups would not have changed (online supplemental table S19 and figure S3). We believe that there is a need to adopt a standard definition of treatment success, so that the studies are better comparable.

The treatment success was corroborated by two objective measurements. Patients after pyloromyotomy, in contrast to patients after the sham procedure, showed significantly improved gastric emptying, even if our results are in line with a lack of consistent reproducible relationships between global GP symptoms and gastric emptying delay.[36]

Pyloromyotomy also increased both pyloric distensibility and cross-sectional area. Unfortunately, Endoflip measurement was started midway through the trial as it was not available when the trial started. Furthermore, two out of three measurements were performed under general anaesthesia with opioids, which could have influenced measured values. Therefore, we cannot draw any firm conclusion with this respect. However, similarly to other two studies, we showed a trend that post-G-POEM distensibility > 13 mm Hg/mm^2 might predict treatment success.[17 37]

We experienced 10 SAEs, but only 3 were related to pyloromyotomy. Even if our results are in line with other studies reporting the occurrence of severe adverse events after G-POEM up to 6%,[38] one case of moderate dumping syndrome in our study and one case report of a severe refeeding syndrome in the literature[39] should be considered when performing pyloromyotomy as this procedure is not free of SAEs. Based on postprocedural symptoms evolution, our patients did not experience new onset or worsening of duodeno-gastric reflux, which is theoretically one of the SAEs with possible long-term sequalae.

Our study has several limitations. First, our follow-up is only 6 months after the procedure, and clinical recurrences may still occur after this time.[14] As such, we continue to follow-up our patients in the absence of further blinding. Longer blinded follow-up was not an option given the severity of the GP symptoms in our patients. Second, with the premature termination of our trial due to the significant results, we did not achieve the planned number of randomised patients. We followed the recommendation of DSMB given the risk of general anaesthesia in patients undergoing sham procedure. The lower number of enrolled patients did not influence the evaluation of the main endpoint but hampers the interpretation of results for the individual types of GP because of a lower number of subjects in postsurgical and idiopathic groups. Third, as we measured gastric emptying at a different time than primary endpoint, we could not accurately assess the relationship between the change in gastric emptying and symptomatic improvement. Future studies should reflect the need to determine the relationship between symptoms and gastric emptying. Fourth, we did not investigate relevant pathophysiological parameters (antroduodenal and small intestinal dysmotility, vagal function), all of which could play a role in development of symptoms or post-G-POEM adverse events. They might also identify a subgroup of patients less likely to respond to the G-POEM procedure. Fifth, all G-POEMs were performed by a single endoscopist, thus, limiting the generalisability of our results.

In conclusion, our results demonstrated that G-POEM is beneficial in a substantial proportion of patients with severe and refractory GP. These results may help expand the range of available treatment options for patients suffering from this debilitating disease. However, our results need to be confirmed, in particular, among patients with idiopathic and postsurgical aetiologies as the results in these two subgroups are not entirely conclusive. Finally, correct patient selection with an emphasis on long-term results should be the focus of future research.

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