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Guillaume Gourcerol, Jean Michel Gonzalez, Bruno Bonaz, Sébastien Fontaine, Frank Zerbib, Francois Mion, Paul Basile, André Gillibert, Amélie Labonde, Heithem Soliman, et al.

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Gastric electrical stimulation versus per-oral pyloromyotomy for the treatment of nausea and vomiting associated with gastroparesis: An observational study of two cohorts

Guillaume Gourcerol[1] | Jean Michel Gonzalez[2] | Bruno Bonaz[3] | Sébastien Fontaine[4] | Frank Zerbib[5] | Francois Mion[6] | Paul Basile[1] | André Gillibert[7] | Amélie Labonde[8] | Heithem Soliman[9] | Véronique Vitton[2] | Benoit Coffin[9] | Jérémie Jacques[8]

[1]Physiology and Gastroenterology Department, INSERM 1073-CIC 1404, RouenUniversity Hospital, Rouen, France

[2]Gastroenterology Department, North Hospital AP-HM, Marseille, France

[3]Gastroenterology Department CHU, Grenoble, France

[4]Diabetology Department CHU, Toulouse, France

[5]Gastroenterology Department, Centre Medico-chirurgical Magellan, INSERM CIC 1401, CHU de Bordeaux, Hôpital Haut-Lévêque, Université de Bordeaux, Bordeaux, France

[6]Physiology Department HCL, Lyon, France

[7]Biostatistic Department, Rouen University Hospital, Rouen, France

[8]CHU, Limoges, France

[9]Gastroenterology Department, Université de Paris, AP-HP, Hopital Louis Mourier, DMU ESPRIT, Colombes, France

Correspondence
Guillaume Gourcerol, Department of Physiology Rouen University Hospital – Charles Nicolle, INSERM UMR-1073-CIC1404, 1 Rue de Germont, 76031 Rouen Cedex, France.
Email: guillaume.gourcerol@chu-rouen.fr

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Abstract

Background: Both gastric electrical stimulation (GES) and gastric-peroral endoscopic myotomy (G-POEM) can be offered to patients with gastroparesis and predominant nausea and vomiting. The study's aim was to compare GES and G-POEM efficacy on nausea and vomiting scores in patients with gastroparesis.

Methods: Two multicenter cohorts of patients with medically refractory gastroparesis with predominant nausea and vomiting (defined as a score >2 on nausea and vomiting subscale that varied from 0 to 4) were treated either with GES ($n = 34$) or G-POEM ($n = 30$) and were followed for 24 months (M). Clinical response was defined as a decrease of ≥1 point in nausea and vomiting subscale without premature exclusion due to switch from one to the other technique before M24. Changes in symptomatic scales and quality of life were also monitored.

Key Results: Patients from both groups were comparable although the mean score of nausea and vomiting subscale was higher in GES (3.0) compared to G-POEM group (2.6; $p = 0.01$). At M24, clinical response was achieved in 21/34 (61.7%) patients with GES and in 21/30 (70.0%; $p = 0.60$) patients with G-POEM. Mean scores of nausea and vomiting subscale decreased at M24 in both GES (from 3.0 to 1.6; $p < 0.001$) and G-POEM (from 2.6 to 1.2; $p < 0.001$) groups, although there was no difference between groups (difference adjusted from baseline: −0.28 [−0.77; 0.19]; $p = 0.24$). Likewise, symptomatic and quality of life scores improved at M24 in both groups, without difference according to treatment group.

Conclusions and Inferences: At M24, we did not observe significant difference in efficacy of GES and G-POEM in medically refractory gastroparesis with predominant nausea and vomiting.

KEYWORDS
chronic nausea and vomiting syndrome, gastric electrical stimulation, gastric emptying, gastroparesis, peroral endoscopic pyloromyotomy

2 | INTRODUCTION

Gastroparesis is a condition characterized by symptomatic delayed gastric emptying (GE) in the absence of mechanical obstruction.[1] Among cardinal symptoms, nausea and vomiting were found to be the most prevalent, and were the predominant symptoms in 24%–44% of cases.[2–4] Gastroparesis-related nausea and vomiting is associated with altered quality of life[4] and health-related costs of up to 4000 and 8000 euros in idiopathic and diabetic gastroparesis, respectively.[5] The therapeutic management of gastroparesis-associated nausea and vomiting remains challenging as less than one third of patients respond to pharmacologic treatment.[6] Recently, two non-pharmacologic options, namely gastric electrical stimulation (GES) and gastric per oral endoscopic myotomy (G-POEM), have emerged to relieve nausea and/or vomiting in refractory gastroparesis.[1]

Gastric electrical stimulation has been shown to decrease medically refractory nausea and/or vomiting associated or not with gastroparesis.[5,7–11] Such an effect has been confirmed in randomized controlled trials, both in patients with and without delayed gastric emptying.[7–11] Of note, GES efficacy targets only nausea and vomiting since other gastroparesis symptoms have not been shown to be relieved by GES in randomized controlled trials.[7–11] This may explain that a subset of patients reports limited or no improvement in different controlled or long-term trials.[8–11] Conversely, G-POEM has recently been developed with the aim to accelerate GE and therefore alleviate gastroparesis-associated symptoms.[12–16] Cohort open-labeled studies reported that 60–80% of patients had symptomatic improvement.[12–17] Recently, G-POEM has been showed to improve gastroparesis symptoms in a randomized controlled study.[18] As a result, GES was considered only in patients with predominant nausea and vomiting, associated or not with delayed GE, while G-POEM was rather considered in symptomatic gastroparesis, regardless of the predominant symptom.[1]

A previous retrospective study suggested that G-POEM was superior to GES for the treatment of symptomatic gastroparesis, regardless of the predominant symptom.[19] Using a propensity score matching that identified 23 patients treated with one or the other technique, authors retrospectively showed that clinical response, defined either as the absence of symptoms recurrence (gastroparesis cardinal symptom index (GCSI) > 2) or the absence of gastroparesis-related hospitalization, was higher with G-POEM than with GES. To date, whether one or the other technique is more effective in gastroparesis associated with medically refractory nausea and vomiting remains unknown. Using data from two cohorts evaluating the effectiveness of GES and G-POEM, respectively, we therefore took the opportunity to assess the efficacy of both techniques to alleviate nausea and vomiting in gastroparesis patients presenting with medically refractory nausea and vomiting.

Key points

- Whether gastric electrical stimulation (GES) or per-oral endoscopic pyloromyotomy (G-POEM) is more effective in gastroparesis with refractory nausea and vomiting remains unknown.
- Symptomatic scores were monitored for 24 months among 2 cohorts of patients treated either with GES or G-POEM.
- At 24 months, we did not observe difference in efficacy of GES and G-POEM.

3 | PATIENTS AND METHODS

This study aggregated data from two independent open-labeled cohorts, namely the Enterra cohort and the G-POEM cohort, that were published individually elsewhere.[5,11,15] The Enterra cohort followed up for 24 months patients with medically refractory nausea and/or vomiting implanted with a GES device, with delayed or normal GE before implantation. The G-POEM cohort followed up for 24 months patients with medically refractory gastroparesis. Both cohorts were conducted in accordance with the principles of the Declaration of Helsinki. Both cohorts were approved by institutional review boards, received ethical agreement (Comité de protection des personnes, under the number No. 2008/019 and No. 342-2019-108, respectively) and were registered as clinical trials (Clinical Trials No. NCT 00903799 and No. NCT04024709, respectively). Last, analysis of both cohorts received the agreement of the local ethics board (Comité d'Ethique pour la Recherche sur Données Existantes: No. E2021-17).

3.1 | Patients

3.1.1 | Enterra cohort

The Enterra cohort included patients with nausea and/or vomiting refractory to medical treatment both with gastroparesis and normal GE[5] from 2009 to 2016. The gastric stimulator and electrodes (Model No. 4300; Medtronic, Boulogne, France) were implanted and stimulation parameters were set up as described previously (frequency 14 Hz; intensity 5 mA; pulse width330 μs; cycle ON 0.1 s; cycle OFF 5.0 s). Of note, during the first 8 months, stimulation parameters were blinded with two successive periods of 4 months with the stimulator randomly turned OFF or ON as reported elsewhere.[11] Gastroparesis symptoms and quality of life were assessed

before stimulator implantation, 12 and 24 months (M12, M24) after implantation.

3.1.2 | G-POEM cohort

The G-POEM cohort included patients with medically refractory gastroparesis from 2017 to 2021.[15] G-POEM procedures were performed under general anesthesia in accordance with the technique previously reported.[12–16] The incision was made on the greater curvature, 3–5 cm from the pylorus. Tunneling was stopped when the typical white pyloric ring was individualized. The myotomy of the pylorus was then performed in a retrograde way. When the myotomy was considered complete (i.e., when the typical aspect of the pink serosa was identified; mean length = 2.5 cm), the tunnel entry was closed with clips. Gastroparesis symptoms and quality of life were assessed before G-POEM, then at M12 and M24 after the procedure.

3.1.3 | Clinical evaluation

In the Enterra and G-POEM cohorts, symptom severity was monitored using the gastrointestinal quality of life index (GIQLI)[20] and GCSI,[21] respectively. Questionnaires were filled by patients with the help of either a study nurse or the investigators. GCSI encompasses nine gastroparesis symptoms (nausea, retching, bloating, gastric fullness, loss of appetite, inability to finish a normal sized meal, stomach visibly larger, and feeling excessively full after a meal) rated from 0 to 5 (0 = absent; 1 = very mild; 2 = mild; 3 = moderate; 4 = severe; 5 = very severe) during the past 15 days. The GIQLI used in the Enterra cohort rated six gastroparesis symptoms (nausea, retching, bloating, gastric fullness, early satiety, and inability to finish a normal sized meal) rated using a 5-point likert scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe) during the past 15 days. In addition, vomiting during the past 15 days was also measured in the Enterra cohort using a similar 5-point likert scale. In order to compare symptom severity in both cohorts, and based on a similar scoring system, we constructed a derived GCSI (dGCSI) based on seven out of the nine symptoms by excluding "stomach visibly larger" and "feeling excessively full after a meal" that were not captured by the GIQLI. Each symptom was rated from 0 to 4 (0 = absent; 1 = mild or very mild; 2 = moderate; 3 = severe; 4 = very severe), the total dGCSI being the mean of each individual symptom and varied therefore from 0 to 4. Comparable to GCSI, dGCSI encompassed three subscales: the nausea and vomiting subscale defined as the mean score of nausea, vomiting, and retching severity; the fullness subscale based on the mean score of gastric fullness, loss of appetite and inability to finish a normal sized meal; the bloating subscale which was identical to the bloating severity score. Quality of life was measured in all patients from the Enterra cohort and in 18/30 patients from the G-POEM cohort. The GE measurement was performed with the technique available in each center, that is scintigraphy or C13 octanoic acid breath test, based either on solid food retention >10% at 4 h or GE half time, respectively.

3.1.4 | Patient selection

All patients enrolled in the Enterra (n = 96) and G-POEM (n = 67) cohorts were eligible for the present study. From these two cohorts, we selected patients with demonstrated gastroparesis using GE test. Patients from both cohorts were refractory to medical treatment, including antiemetics and prokinetics. In all patients, mechanical obstruction was ruled out by an upper gastro-intestinal endoscopy. Patients with prior gastric surgery were not considered for the study, with the exception of anti-reflux surgery. Patients with prior intrapyloric administration of botulinum toxin in the previous 6 months, and patients under opioids were also not considered for the study. In addition, only patients with predominant nausea and/or vomiting, defined as a nausea and vomiting score of ≥2, were considered. A flowchart reporting patient selection is provided in Figure 1. Of note, 31/96 patients from the Enterra cohort had normal GE before implantation, according to patient selection in the Enterra study.[15] As expected, none of the G-POEM patients had normal GE at baseline; also, 26/67 patients from the G-POEM cohort and only 18/96 patients from the Enterra cohort had a nausea and vomiting score of <2. The number of patients with missing data recorded at M24 (lost to follow-up, death, consent withdrawal, etc.) was comparable in both cohorts (12/46 in the Enterra cohort versus 11/41 in the G-POEM cohort). Final analysis was therefore carried out in 30 patients treated with G-POEM and 34 patients treated with Enterra. Of note, one patient reported pregnancy before GES implantation and was therefore not considered for either final or intention to treat (ITT) analysis.

3.1.5 | Primary and secondary endpoints

The clinical response was defined as: (1) a decrease of ≥1 point in the nausea and vomiting score of the dGCSI scale at M24 and (2) the absence of switch from one to the other technique before M24. Other endpoints included changes in dGCSI scale, dGCSI subscales, and GIQLI scale. ITT analysis was also carried out by including patients lost to follow-up, serious adverse events, death unrelated to the procedures and consent withdrawal.

3.1.6 | Statistical analysis

All quantitative variables were described by means and standard deviations except the duration of disease that was expected to be highly skewed and was described by the median and quartiles. All qualitative variables were described by frequencies and percentages. Means, medians, and percentages of baseline variables were respectively compared between groups, by two-sample Student t tests, Mann–Whitney test and Fisher's exact tests.

Missing data of variables with <20% of missing data in both groups were simply imputed by the predicted probability of logistic regressions (with a probability cut-off at 0.50) for binary

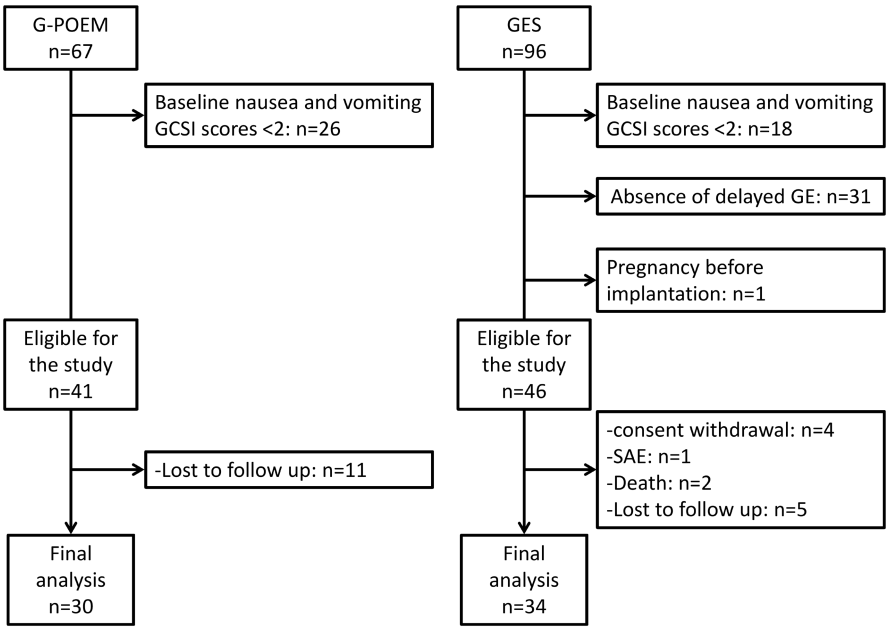

FIGURE 1 Study flow chart. GCSI, gastroparesis cardinal symptom index; GE, gastric emptying; GES, gastric electrical stimulation; G-POEM, gastric per-oral endoscopic myotomy; SAE, serious adverse event.

variables and by the predicted value of Gaussian linear models for quantitative variables. The following variables were used for imputation: dGCSI subscale at baseline for each dGCSI subscale at M12 and at M24; weight and dGCSI at baseline for the variable "weight loss ≥ 10%"; the weight for the height; dGCSI at baseline for disease duration, associated conditions (diabetes and anti-reflux surgery), and GIQLI at baseline. The total dGCSI score was computed as the mean of the three subscales weighted by their number of items (3 for nausea/vomiting, 3 for fullness/early satiety, 1 for bloating). GIQLI at M12 and M24 had missing data in the G-POEM group; therefore, multiple imputation by chained equations was carried out with predictive mean matching models based on core variables (dGCSI at M12 and M24 and the intervention group). The frequency of missing data was described in each group (G-POEM and GES) for all variables.

Changes in dGCSI, its subscales and GIQLI were compared between G-POEM and GES at M24 in general linear models with a linear adjustment on the baseline scale or subscale. For GIQLI, a multiple imputation procedure was used, with Rubin's rule for variance pooling. All tests were two-sided at the 5% significance threshold without multiple testing procedure. All analyses were performed in R statistical software (version 4.0.3, The R Foundation for Statistical computing, Vienna, Austria).

4 | RESULTS

4.1 | Patients' characteristics at baseline

A total of 30 patients with G-POEM and 34 patients with GES were included in analyses (Figure 1). Patients' characteristics after simple imputation are described in Table 1. The sex ratio, mean age, mean body mass index, and frequency of conditions associated with gastroparesis were not significantly different between groups. The median duration of disease at baseline was significantly shorter for GES (34 months, interquartile range (IQR): 18–52) than for G-POEM (57, IQR: 30–91, $p = 0.02$). Of note, the mean d-GCSI symptom severity was not significantly different between GES and G-POEM treated patients, although the mean [SD] score of the nausea and vomiting subscale was higher in patients treated with GES (3.0 [0.7]) compared to patients treated with G-POEM (2.6 [0.6], $p = 0.01$). The mean quality of life measured according to the GIQLI scale was significantly worse in the GES group (52 [23]) than in the G-POEM group (70 [18]; $p = 0.001$).

4.2 | Clinical response

Clinical response was observed in 21/34 (61.7%) patients treated with GES and 21/30 (70%; $p = 0.60$) patients treated with G-POEM. Among the 13 failures with GES, 8 were related to a decrease of <1 point in the nausea and vomiting score of the dGCSI scale, and 5 to a stability or worsening of nausea and vomiting. Among the nine failures with G-POEM, five were related to a decrease of <1 point in the nausea and vomiting score of the dGCSI scale, three to a worsening of nausea and vomiting, and one patient underwent GES due to G-POEM symptomatic inefficacy before M12. There were no serious adverse events leading either to exclusion before M24 or to failure at M24 in both groups.

In both groups, dGCSI scores and its subscores all improved at M12 and M24 compared to baseline (Figure 2). Likewise, severity of nausea, retching, and vomiting also improved at M12 and M24 in both groups (Figure 3). However, no difference was observed between GES and G-POEM for changes in dGCSI scale, dGCSI subscales, and symptom severity (Figures 2, 3). Comparably, GIQLI improved in both groups compared to baseline, but no difference was seen in the magnitude of improvement between GES and G-POEM (Figure 4).

TABLE 1 Patients' characteristics at baseline.

	GES	G-POEM	*p*
n	34	30	
Age (years), mean (SD)	45.9 (12.9)	50.6 (14.7)	0.17
Female sex, *n* (%)	26 (76.5%)	21 (70.0%)	1.00
BMI (kg/m^2), mean (SD)	23.4 (5.1)	23.3 (5.4)	0.90
Disease duration (months), med (IQR)	34 (18, 52)	57 (30, 91)	0.02*
Weight loss >10%, *n*, (%)	21 (61.8%)	15 (50%)	0.49
Diabetes, *n* (%)	10 (29.4%)	10 (33.3%)	0.94
Anti-reflux surgery, *n* (%)	8 (23.5%)	4 (13.3%)	0.47
dGCSI, mean (SD)	3.1 (0.5)	2.9 (0.5)	0.14
Bloating subscore, mean (SD)	3.1 (0.7)	3.1 (0.9)	0.87
Fullness subscore, mean (SD)	3.1 (0.8)	3.0 (1.1)	0.72
Vomiting subscore, mean (SD)	3.0 (0.7)	2.6 (0.6)	0.01*
Nausea score (SD)	2.8(1.3)	3.0 (0.9)	0.83
Retching score (SD)	3.1(0.9)	2.7(1.2)	0.16
Vomiting score (SD)	3.0 (1.3)	2.2 (1.4)	<0.01
GIQLI, mean (SD)	52 (23)	70 (18)	0.001*

Abbreviations: BMI, Body mass index; dGCSI, derived gastroparesis cardinal symptom index; GIQLI, gastrointestinal quality of life index; IQR, interquartile range; SD, standard deviation.

*Statistically significant at 5% significance threshold.

Intention to treat analysis found 21 (46%) clinical response in the GES treated group, and 25 failures, including 13 score changes of<1 point in the nausea and vomiting subscale at M24, 4 consent withdrawals, 5 lost to follow-up, 2 deaths, and 1 serious adverse event unrelated to GES (Figure 1). ITT analysis identified 21/41 (51%; $p = 0.67$) clinical response in patients treated with G-POEM. The 20 failures included 8 score changes of <1 point in the nausea and vomiting subscale, 1 patient switched to GES before M12 due to inefficacy, and 11 patients lost to follow-up (Figure 1).

5 | DISCUSSION

Gastroparesis is morbid condition associated with increased mortality, altered quality of life, and increased healthcare-related costs.[5,22–24] Accordingly, patients are willing to accept therapeutic strategies associated with significant risks of side effects.[25] As a result, GES may be offered to most severe patients with intractable nausea and vomiting.[1] Likewise, G-POEM has recently emerged as new alternative therapeutic tool to treat patients with medically refractory gastroparesis.[18] In the present study, we have shown that GES and G-POEM efficacy was not different to relieve symptoms of nausea and vomiting in gastroparetic patients. Indeed, both GES and G-POEM led to an at least 1-point decrease in the nausea and vomiting score of the dGCSI scale at M24 in 61.7 and 70% of patients, respectively. Last, other symptomatic subscales and the quality of life were improved at M24 in patients treated either with GES or

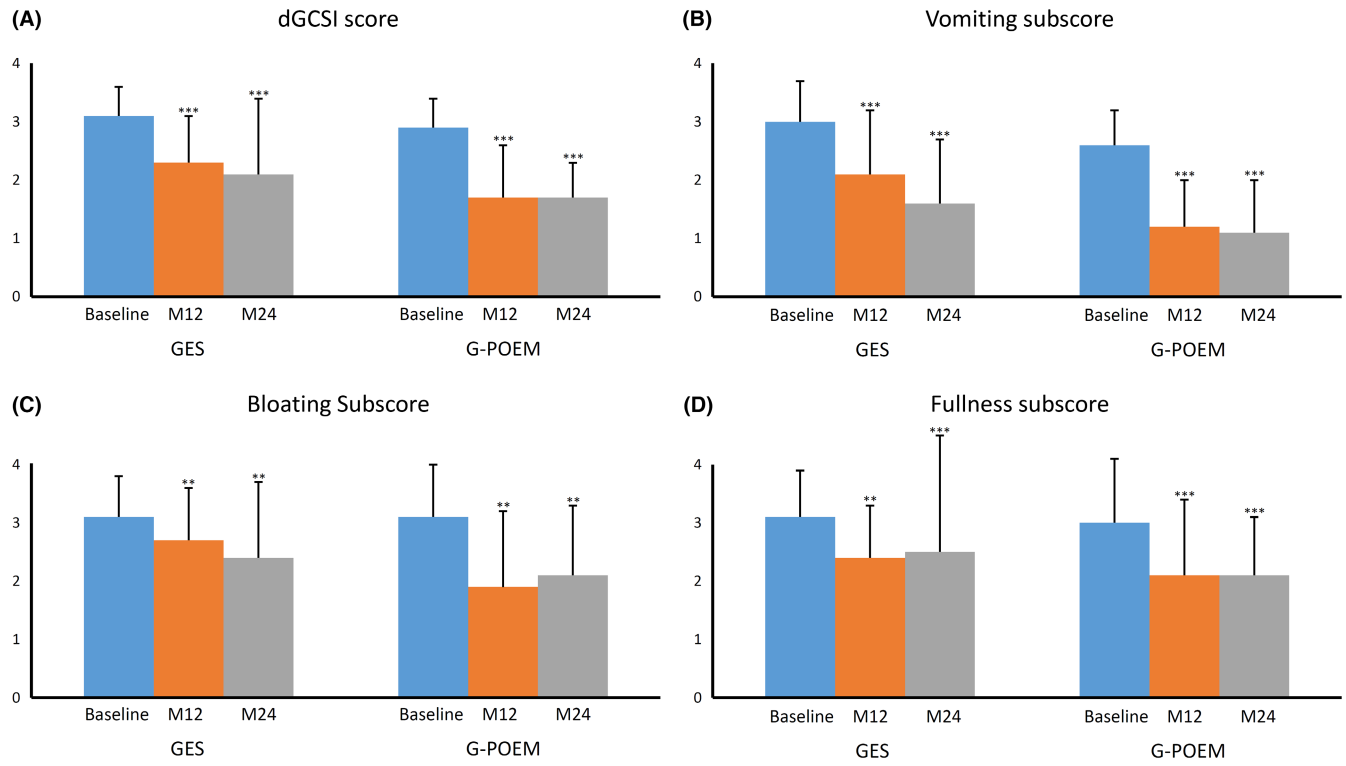

FIGURE 2 dGCSI score (A), vomiting (B), bloating (C), and fullness (D) subscores at baseline, 12 months (M12) and 24 months (M24) after gastric electrical stimulation (GES) or gastric per-oral endoscopic myotomy (G-POEM). $^{**}p < 0.01$ versus baseline; $^{***}p < 0.001$ versus baseline.

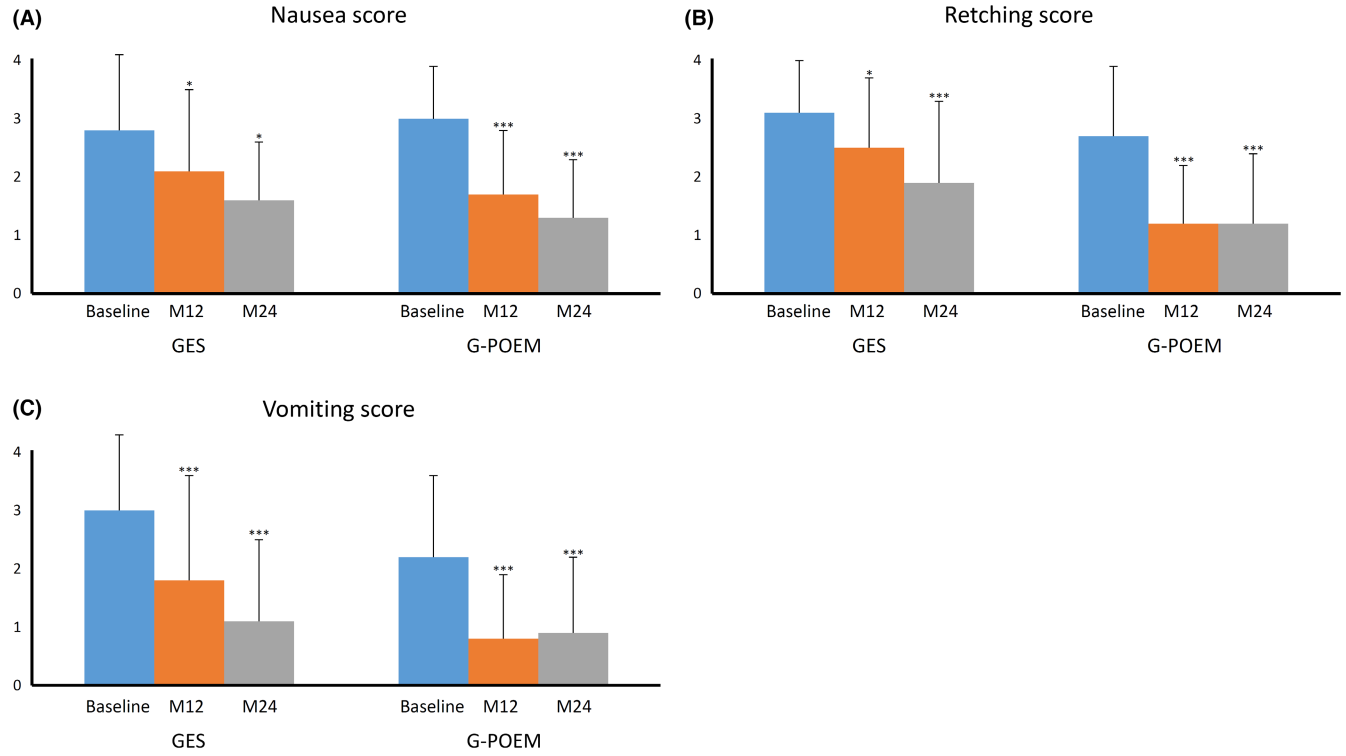

FIGURE 3 symptomatic scores of nausea (A), retching (B) and vomiting (C) at baseline, 12 months (M12) and 24 months (M24) after gastric electrical stimulation (GES) or gastric per-oral endoscopic myotomy (G-POEM). *$p < 0.05$ versus baseline; ***$p < 0.001$ versus baseline.

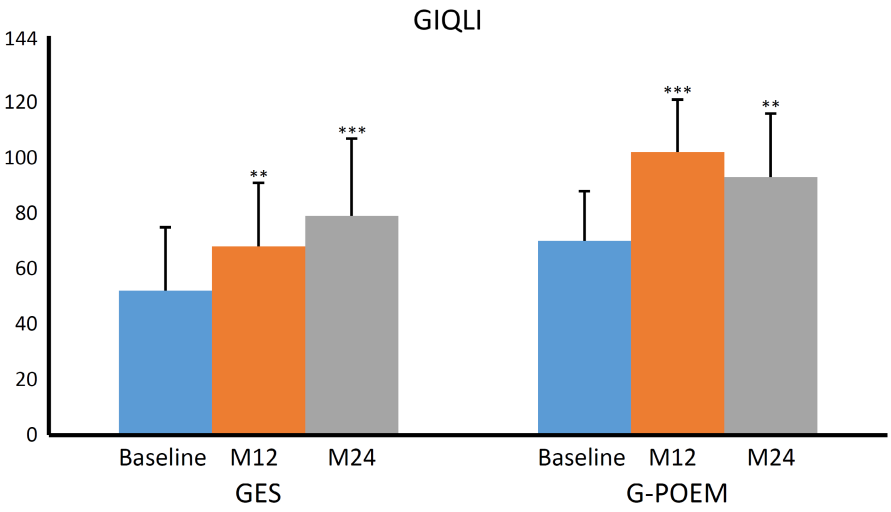

FIGURE 4 GIQLI at baseline, baseline, 12 months (M12) and 24 months (M24) after gastric electrical stimulation (GES) or gastric per-oral endoscopic myotomy (G-POEM). **$p < 0.01$ versus baseline; ***$p < 0.001$ versus baseline.

G-POEM, although the magnitude of improvement was not different between groups.

To date, only one retrospective study by Shen et al.[19] including 23 patients in each group, has compared G-POEM and GES to alleviate gastroparesis overall symptoms. Of note, the overall success rate was comprised between 50 and 70%, which was comparable to our study. However, the superiority of G-POEM compared to GES in this study was not unexpected since GES has been shown to be only effective to relieve nausea and vomiting.[15] Our study was therefore at variance with the Shen et al.[19] study. First, we specifically addressed gastroparesis with predominant nausea and vomiting. Indeed, GES alleviates only nausea and vomiting, while other symptoms of gastroparesis are classically not improved using this technique. Therefore, comparing GES and G-POEM may be seen as more relevant in this specific group of patients. In addition, the main endpoint in our study was defined as the decrease at M24 of the nausea and vomiting subscore, while treatment efficacy combined symptomatic scores and time to first gastroparesis-related hospitalization in the Shen et al. study. Interestingly, treatment efficacy in the study from Shen et al. was associated with the etiology of gastroparesis. In fact, we have shown that the rate of hospitalization differed, before but also after GES, according to the diabetic or non-diabetic origin of

gastroparesis.[5] Of note, Shen et al. identified 26% of adverse events related to GES while they observed only 4% of adverse events in the G-POEM treated group. In our hands, GES-related adverse events were <10% with a need for device removal in <2%.[15] Altogether, and despite their differences, both studies may be seen as complementary. Indeed, our study suggested that GES and G-POEM have similar efficacy in nausea and vomiting predominant gastroparesis, while the Shen et al. study suggested that G-POEM may be more effective in the treatment of other symptoms of gastroparesis. A recent report compared GES to surgical pyloromyotomy or pyloroplasty in patients with gastroparesis regardless of dominant symptoms.[26] Authors found that GES and pyloric surgeries led to a similar improvement in GCSI score, although GES achieved a better relief of nausea and vomiting symptoms. A second recent report by Marowski et al.[27] also compared GES to surgical pyloromyotomy. Again, this study included patients with gastroparesis regardless of dominant symptoms. In contrast with the work of Shen et al.[19] and comparable with the present study, the study of Marowski et al.[27] did not evidence major differences in the efficacy of both techniques, with an overall efficacy of 72% at M12. In clinical practice, our study provided therefore clues to use one or the other technique in gastroparesis with predominant nausea and/or vomiting, although future randomized studies are therefore warranted to confirm these conclusions.

Whether a combination of G-POEM and GES is more effective than one or the other technique alone is currently not known. Theoretically, pharmacologic acceleration of gastric emptying in patients with gastroparesis is expected to be associated with symptom relief although this statement has not been firmly ascertained.[28–32] Nevertheless, the superiority of a GES/G-POEM combination treatment could be speculated since both techniques act through different pathways. GES has been shown to relieve nausea and vomiting through central pathway,[33–35] without accelerating gastric emptying.[36–38] Likewise, GES has been shown to be effective in both patients with delayed or normal gastric emptying prior implantation.[37–39] In contrast, G-POEM accelerates gastric emptying by increasing pylorus diameter and distensibility.[12,40–44] A first cohort study of combined GES and surgical pyloroplasty (n = 24) found a 71% efficacy with a mean follow-up of 17 months.[45] In two recent comparative studies, GES associated with surgical pyloroplasty did not lead to better outcome than GES or surgical pyloroplasty alone.[26,27] To date, only one study has reported the outcome of combined GES and G-POEM in 24 patients with refractory gastroparesis.[46] Short-term outcome analysis showed an improvement of GCSI score and subscores of all symptoms. Of note, none of these reports addressed specifically the subgroup of nausea and vomiting gastroparesis, although nausea and vomiting subscores improved in all these cohort studies after treatment with a combination of GES and G-POEM.

Our study was not without limitations. First, patients' severity was different at baseline. Indeed, nausea and vomiting subscores were higher while quality of life was worse at baseline in the group treated with GES compared to the group treated with G-POEM. It is noteworthy that other characteristics were comparable. However, although significant, the difference in nausea and vomiting subscores at baseline may be considered as marginal since the difference in median (3.0 vs. 2.7) and mean scores (3.0 vs. 2.6) was <0.4 while an improvement of at least one point was expected and a 1.5 to 2.0 point improvement was observed. In addition, efficacy, based on the magnitude of improvement was not different between groups using adjusted analysis. Another limitation of the present study was related to the lack of randomization and blinding. Based on our data, and using a similar primary endpoint, we calculated that a total number of 1368 patients would be necessary to observe a difference with a power of 90%. When considering that our study was conducted only in a subgroup of patients with gastroparesis (with predominant nausea and vomiting) or a chronic nausea and vomiting syndrome (associated with delayed GE), this calculation outlines the difficulty to set up such long-term randomized comparative trials. A last limitation was the symptomatic scale we used. In fact, the GCSI scale was not used in the GES cohort, as this scale was not developed at the time the cohort started. However, the symptomatic questionnaires we used were in fact almost identical to GCSI, except for two symptoms that were missing and a 4-point likert scale that did not distinguish between "mild" and "very mild". We doubt this may have explained differences in baseline nausea and vomiting scores since quality of life was also worse at baseline in the GES group, and this may be related to some extent to the severity of nausea and vomiting. Our study also has strengths, including the multicenter nature of data collection, and was to our knowledge the most powered with a total of 64 patients. Last, the fact that we chose to study a subgroup of patients with gastroparesis and predominant nausea and vomiting allowed a relevant comparison between the two techniques that are used in clinical practice in different patient populations.

In conclusion, our study suggested that clinical response between GES and G-POEM at M24 was not different to relieve nausea and vomiting in patients with medically refractory nausea and vomiting associated with gastroparesis.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

Guillaume GOURCEROL received consulting fees from Takeda, Kyowa Kyrin and Allergan. GG served as a speaker for Laborie, Biocodex. Bruno BONAZ received consulting fees from Janssen and Abbvie. Jean Michel GONZALEZ received consulting fees from Ambu; Boston Scientific. Paul BASILE served as a speaker for Life Partner Europe, Norgine and Tillots Pharma, and received support for attending meetings from Amgen, Norgine, Mayoloy Spindler, Covidien AG and Boston Scientific. Jérémie JACQUES served as a speaker for ERBE Medical. Sébastien FONTAINE, Frank ZERBIB, Francois MION, André GILLIBERT, Amélie LABONDE, Heithem SOLIMAN, Véronique VITTON and Benoit COFFIN have no conflict of interest.

ORCID

Guillaume Gourcerol https://orcid.org/0000-0001-8220-9155
Bruno Bonaz https://orcid.org/0000-0003-1858-8941
Frank Zerbib https://orcid.org/0000-0002-6802-2121
Francois Mion https://orcid.org/0000-0002-2908-1591
Benoit Coffin https://orcid.org/0000-0002-0606-4158

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