



# Gastric peroral endoscopic myotomy versus botulinum toxin injection for the treatment of refractory gastroparesis: results of a double-blind randomized controlled study

## Authors

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## ABSTRACT

**Introduction** Gastric peroral endoscopic myotomy (G-POEM) is a promising technique for treating refractory gastroparesis. We present the first double-blind randomized study comparing the clinical efficacy of G-POEM versus pyloric botulinum toxin injection (BTI).

**Methods** This randomized study, conducted in two expert centers, enrolled patients with refractory gastroparesis, medically managed for >6 months and confirmed by gastric emptying scintigraphy (GES), into two groups, G-POEM versus BTI, with follow-up of 1 year. The primary end point was the 3-month clinical efficacy, defined as a >1-point decrease in the mean Gastroparesis Cardinal Symptom Index (GCSI) score. Secondary end points were: 1-year efficacy, GES evolution, adverse events, and quality of life.

**Results** 40 patients (22 women; mean age 48.1 [SD 17.4]), with mean symptom duration of 5.8 (SD 5.7) years, were randomized. Etiologies included idiopathic (n=18), diabetes (n=11), postoperative (n=6), and mixed (n=4). G-POEM showed a higher 3-month clinical success than BTI (65% vs. 40%, respectively;  $P=0.10$ ), along with non-significantly higher 1-year clinical success (60% vs. 40%, respectively) on intention-to-treat analysis. The GCSI decreased in both groups at 3 months and 1 year. Only three minor adverse events occurred in the G-POEM group. The GES improvement rate was 72% in the G-POEM group versus 50% in the BTI group (non-significant).

**Conclusion** G-POEM seems to have a higher clinically relevant success rate than BTI, but this was not statistically demonstrated. This study confirms the interest in treatments targeting the pylorus, either mechanically or chemically, for managing refractory gastroparesis.

## Introduction

Gastroparesis is defined as epigastric symptoms and delayed gastric emptying in the absence of mechanical obstruction [1]. Epidemiological studies estimate the prevalence in the general population to be approximately 24.2 persons per 100000, with a female predominance [2, 3]. The diagnosis is based on a combination of evocative nonspecific clinical symptoms, the ab-

sence of lesions on upper gastrointestinal endoscopy, and the results of gastric emptying scintigraphy [1]. The three main etiologic categories described are diabetic, idiopathic, and postoperative, accounting for more than three-quarters of gastroparesis cases [4].

The severity of the disease is assessed using a clinical score: the Gastroparesis Clinical Symptom Index (GCSI). This includes nine symptoms, divided into three subscales: vomiting, satiety,

and bloating [5,6,7]. Classical management of gastroparesis includes dietary changes and medical therapy with prokinetics (domperidone, erythromycin) to stimulate gastric peristalsis, but treatment is frequently disappointing, insufficient, and associated with adverse events (AEs) [1,8]. Gastric electrical stimulation has also been proposed in various protocols, but clinical improvement was not shown, except in vomiting patients [9,10,11]. Moreover, being expensive and requiring surgical intervention, it is not currently routinely proposed, except in a few countries such as the USA.

With regard to the pathophysiology, which is complex and still debated, there is a combination of at least two components: an impairment of antral motricity through a decrease in the number of interstitial cells regulating gastrointestinal contractions and/or a reduced pyloric myorelaxation leading to pylorospasm, which slows down gastric emptying [12,13,14]. For these reasons, and because of the disappointing efficacy of medical therapies, endoscopic treatments targeting the pylorus have been proposed, among them botulinum toxin injections (BTI) and gastric peroral endoscopic myotomy (G-POEM).

Despite two initial open-label studies of BTI that showed efficacy around 70%, two randomized studies concluded that the efficacy was not sustained over time and no different to placebo [7,15,16,17]. It was therefore not included in the last ESGE recommendations [18].

G-POEM was described a few years ago and has demonstrated very promising results in improving gastroparesis symptoms in several studies [19,20,21,22,23,24]. Two recent meta-analyses and a large French multicenter study recently confirmed these outcomes, showing an efficacy rate at 1 year of around 65%, with a very low rate of AEs [25,26,27]. Therefore, ESGE has proposed G-POEM as a therapeutic alternative on the condition that the gastroparesis is confirmed by gastric emptying scintigraphy (GES), classified as severe (defined as GCSI >2), refractory to other treatments, and that the procedure is performed in an expert center [18]. Very recently, two important prospective studies have been published. The first one was conducted by Vosoughi et al. on 80 patients and demonstrated a 12-month efficacy rate of 56%, using a very strict efficacy definition [28]. The second was a randomized trial published by Martinek et al. comparing G-POEM versus placebo in 40 patients, which demonstrated an efficacy rate at 1 year of around 70%, confirming the previous results [29].

We present the results of the first randomized controlled study comparing G-POEM versus BTI for the treatment of refractory gastroparesis.

## Methods

### Design and inclusion

This was a prospective randomized double-blind study, conducted between September 2016 and May 2019. Two centers with experts in submucosal endoscopy and functional diseases were involved: the Hôpital Nord in Marseille and the Hôpital Édouard Herriot in Lyon, France. Patients or public were not involved in the design, conduct, reporting, or dissemination plans of our research. The randomization had been established

before the implementation of the study, under the responsibility of the project's referent methodologist (K.B.), with the method chosen being blocks of four patients permuted by stratum, with a 1:1 randomization. The allocation of the intervention group was contained in a sealed envelope, which was opened at the moment of inclusion to avoid selection bias.

The inclusion criteria were: age over 18 years; gastroparesis evolving for more than 1 year that was refractory to optimal medical treatment (prokinetics including erythromycin) attempted for more than 6 months, severe with a preinclusion GCSI score >2, confirmed by a recent (<3 months) GES showing either increased half-emptying time and/or increased residual percentages at 2 and 4 hours; no history of gastric surgical resection (partial gastrectomy, sleeve gastrectomy); a recent (<3 months) normal upper gastrointestinal endoscopy (no antropeptic ulcer, cancer); signed informed consent provided; and affiliation to a health insurance system in France. Radiolabeled GES was performed according to the consensus of the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine [30].

Non-inclusion criteria were: age <18, pregnancy or breastfeeding, presence of an anesthetic contraindication, use of curative dose anticoagulants or double antiplatelet medication where suspension was contraindicated, and inability to provide informed consent.

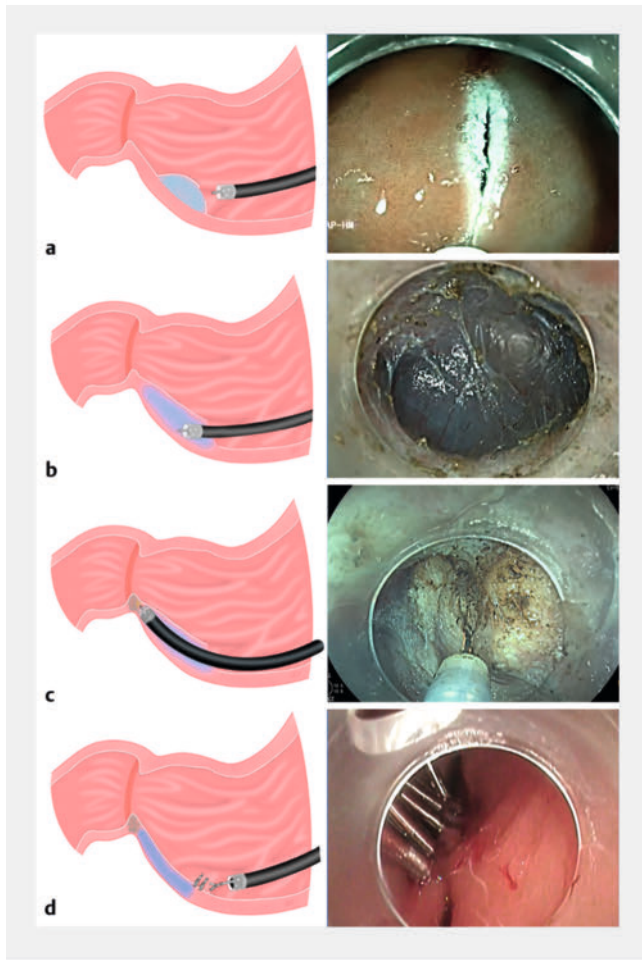
Enrolment was carried out after medical visits and a regulation cooling-off period. A pre-randomization list had been established, with the patients being distributed into two therapeutic groups: G-POEM or BTI.

### Procedures and follow-up

All procedures were performed, with the patient under general anesthesia and intubated, by one of four interventional endoscopists (two per center) who were experts in POEM (>100 cases each). The botulinum toxin used was Botox (Allergan laboratories, Courbevoie, France). BTI was conducted as recommended and used in most studies [16,18]: 200IU were injected into four quadrants of the pylorus, using a 23-gauge injection needle. G-POEM was performed according to the following steps: (i) submucosal injection of blue saline into the posterolateral part of the antrum, 5 cm upstream from the pylorus; (ii) mucosal incision using a knife (Dual or Triangle knife) application of Endocut current; (iii) submucosal dissection up to the pyloric arch; (iv) retrograde myotomy of the pyloric muscle and the antrum within 2 cm; (v) closure of the mucosal defect with endoclips. The procedural steps are illustrated in ► **Fig. 1**. Patients were blinded from the procedure they underwent.

After the procedure, all patients were hospitalized, kept fasting through the night following the intervention, and commenced on proton pump inhibitor (PPI) therapy. In the absence of an AE, they were gradually refeed following a standardized protocol: liquids on postoperative day 1 and then a soft diet for 1 week. They were discharged on postoperative day 3 or 4, with a prescription of PPIs for 2 months postoperatively.

The follow-up is summarized in **Fig. 1s**, see online-only Supplementary material. Patients were blindly assessed by gastroenterologists who did not perform the procedure. Visits were



► **Fig. 1** Illustrations and endoscopic views of the main procedural steps of gastric peroral endoscopic myotomy (G-POEM) showing: **a** submucosal injection and mucosal incision at the posterior part of the antrum, 4–5 cm upstream from the pylorus; **b** tunneling by submucosal dissection using the Triangle-tip Knife (Olympus, Japan) up to the pyloric arch; **c** complete retrograde myotomy of the pylorus; **d** mucosal closure using through-the-scope endoclips.

carried out at 1 month (AEs), 3 months, 6 months, and 12 months. At each visit the data recorded were: the GCSI score, Medical Outcomes Study Short-Form General Health Survey-12 (SF-12) score, Gastrointestinal Quality of Life Index (GIQLI) score, body mass index, and any AEs that had occurred. At 3 months, GES was performed to evaluate the evolution of gastric emptying, including the half-emptying time and residual percentages at 2 and 4 hours. At the end of follow-up, patients were informed of which intervention they had received, and could then benefit from the other one if they requested. All patient data were collected on paper case report forms.

## Objectives

The primary end point was the clinical efficacy of G-POEM compared with BTI at 3 months, assessed by the GCSI score. Clinical efficacy was defined as a significant decrease of  $>1$  point in the mean GCSI score compared with the initial preoperative assessment, as proposed in recent series [25,31].

The secondary end points were to compare across the two groups: (i) clinical efficacy, applying the initial definition, represented by a decrease in the GCSI score of 0.6 points from baseline; (ii) clinical efficacy at 1 year (GCSI decrease  $>1$ ); (iii) improved quality of life, based on the SF-12 and GIQLI scores; (iv) improvement in the main GES findings (half-emptying time, solid residual activity at 2 and 4 hours), meaning either normalization or  $\geq 50\%$  decrease in the gastric half-emptying time and/or the residual percentages (normal values: half-emptying time, 145 minutes; 2-hour residual, 60%; 4-hour residual,  $<10\%$ ) [32,33]; (v) the rate of AEs, graded with the AGREE classification, and their management.

## Ethical statement

The study was approved on 9 November 2016 by the ethical review board “Comité de Protection des Personnes Sud-Méditerranée I,” with the IRB-ID: 2016-A01365–46 and the internal reference number: 1694. We confirm that written informed consent was obtained from each patient. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the institution's human research committee.

## Statistical analysis

The calculation of the number of subjects was based on assumptions made around the primary end point, namely the GCSI score [5,6]. These hypotheses were essentially based on the Enterra study [34] concerning the evaluation of gastric electrical stimulation, which reported a decrease of 0.6 points on average (SD 0.2) between the initial evaluation and the evaluation at 3 months, a decrease that was considered to be effective within the framework of the present project. Moreover, we hypothesized that the experimental group (G-POEM) would reach a clinical efficacy rate of 80% (according to the definition above) at 3 months [22,23], whereas we expected efficacy to be around 40% in the control group [16,17]. According to this hypothesis, with a power of 80% and an alpha risk of 5% (unilateral situation), 19 patients per group were necessary. We therefore included 40 subjects.

Statistical analyses were carried out with SPSS software (IBM, USA). Analysis was based on the intention-to-treat (ITT) population (primary analysis), excluding patients with a major protocol violation (no objective post-inclusion data). The scores of the different standardized questionnaires were calculated according to the algorithms provided by the scale developers (GCSI, SF-12, GIQLI). Descriptive analysis of the entire sample was presented per group (G-POEM, BTI). The rate of clinical efficacy at 3 months (primary end point) was compared between the groups (chi-squared or Fisher exact test); data were presented as numbers, rates, difference and 95%CI. The secondary end points were compared between groups according to the nature of the variable (chi-squared or Fisher exact test for qualitative variables; Student's *t* test or Mann–Whitney test for quantitative variables).

Four potential predictive factors of 3-month clinical efficacy according to the literature [25,28] were tested: duration of symptoms before inclusion (months), etiology of gastroparesis

► **Table 1** Baseline characteristics of patients in the gastric peroral myotomy (G-POEM) and botulinum toxin injection (BTI) groups.

|   | G-POEM        | BTI          |
|---|---------------|--------------|
| Sex, male, n (%)  | 6 (30)        | 12 (60)      |
| Etiology, n (%)   |               |              |
| ▪ Idiopathic  | 11 (55)       | 7 (35)       |
| ▪ Diabetic  | 4 (20)        | 7 (35)       |
| ▪ Post-operative  | 2 (10)        | 4 (20)       |
| ▪ Connective tissue disorder                                      | 0             | 1 (5)        |
| ▪ Mixed (diabetic + post-op)                                      | 3 (15)        | 1 (5)        |
| Age, mean (SD), years   | 46.2 (19.3)   | 49.9 (15.6)  |
| BMI, mean (SD), kg/m <sup>2</sup>                                 | 23.3 (3.7)    | 21.0 (3.9)   |
| Duration of symptoms, mean (SD), years                            | 5.3 (4.0)     | 6.4 (7.1)    |
| GCSI score, mean (SD)   | 3.6 (0.7)     | 3.3 (1.0)    |
| SF-12 score, mean (SD)  | 35.2 (4.9)    | 38.5 (5.2)   |
| GIQLI score, mean (SD)  | 53.4 (17.4)   | 60.7 (20.1)  |
| Gastric emptying scintigraphy                                     |               |              |
| ▪ Half-emptying time, mean (SD), minutes                          | 273.0 (176.9) | 205.6 (68.0) |
| ▪ 2-hour residual solid activity, mean (SD), %                    | 69.3 (24.5)   | 75.7 (14.4)  |
| ▪ 4-hour residual solid activity, mean (SD), %                    | 43.3 (28.9)   | 40.1 (20.9)  |
| Albumin, mean (SD), g/L   | 41.3 (2.6)    | 39.6 (5.9)   |
| BMI, body mass index; GCSI, Gastroparesis Cardinal Symptom Index. |               |              |

(diabetes vs. others), 4-hour residual during GES upon inclusion, and 1-month satiety subscale (lower or greater than 3.5). The results were presented as an odds ratio (OR) and 95%CI.

## Results

### Population

In total, 45 patients were initially screened, among whom two did not meet the inclusion criteria, and three refused to be involved. Therefore, 40 patients were included, 20 per group and per center between April 2017 and June 2020. There were 22 women and 18 men, with a mean age of 48.1 (SD 17.4) years. The patients had been suffering from symptoms of gastroparesis for 5.8 (SD 5.7) years. The etiology of the gastroparesis was idiopathic in 18 patients, diabetes in 11, postoperative in six, related to systemic disease in one, with four patients having a mixed postoperative and diabetic etiology. The characteristics and GCSI scores of the included patients are detailed in ► **Table 1** and ► **Table 2**. SF-12 scores at inclusion were significantly lower in the G-POEM group than in the BTI group (35.2 [SD 4.9] vs. 38.5 [SD 5.2];  $P=0.02$ ). There was no difference in the

► **Table 2** Baseline Gastroparesis Cardinal Symptom Index (GCSI) subscales of patients in the gastric peroral myotomy (G-POEM) and botulinum toxin injection (BTI) groups. All values are given as mean (SD).

|                                    | G-POEM           | BTI              |
|------------------------------------|------------------|------------------|
| Nausea                             | 3.6 (1.5)        | 3.4 (1.7)        |
| Retching                           | 2.8 (1.7)        | 3.1 (1.8)        |
| Vomiting                           | 2.6 (1.9)        | 2.3 (2.1)        |
| Vomiting subscale                  | 3.0 (1.4)        | 2.9 (1.5)        |
| ▪ Early satiety                    | 4.2 (1.2)        | 3.7 (1.2)        |
| ▪ Not able to finish a normal meal | 4.4 (0.7)        | 3.7 (1.6)        |
| ▪ Post-prandial fullness           | 4.4 (0.8)        | 4.2 (1.2)        |
| ▪ Loss of appetite                 | 3.0 (1.5)        | 2.6 (2.1)        |
| Satiety subscale                   | 3.9 (0.7)        | 3.6 (1.3)        |
| ▪ Bloating                         | 4.0 (1.3)        | 3.7 (1.9)        |
| ▪ Stomach/belly visibly larger     | 3.8 (1.5)        | 3.8 (2.0)        |
| Bloating subscale                  | 3.9 (1.3)        | 3.3 (1.8)        |
| <b>Total GCSI score</b>            | <b>3.6 (0.7)</b> | <b>3.3 (1.0)</b> |

mean hospital stay between the two groups (3.2 versus 3.0 days).

During the follow-up period, three patients were lost to follow-up by 3 months in the BTI group. At 1 year, five more patients had been lost to follow-up, two in the G-POEM group and three in the BTI group (► **Fig. 2**).

### Primary end point: 3-month clinical efficacy

At 3 months, all patients in the G-POEM group and 17 patients in the BTI group (85%) were included for analysis. In per-protocol (PP) analysis, the clinical efficacy rate reached 65% ( $n=13/20$ ) for G-POEM versus 47% ( $n=8/17$ ) for BTI. On ITT analysis, the rate of clinical efficacy was 65% versus 40%, respectively (95%CI -0.16 to 0.48;  $P=0.10$ ) (► **Table 3**).

Additionally, the mean delta of GCSI improvement between inclusion and 3 months was 1.5 (SD 1.2) in the G-POEM group compared with 1.2 (SD 1.2) in the BTI group ( $P=0.32$ ).

### Secondary end points

#### Clinical efficacy at 3 months with GCSI improvement >0.6

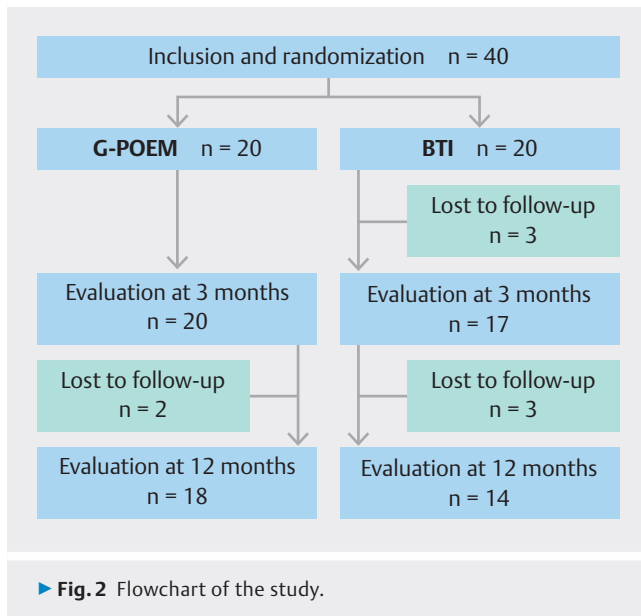
When applying the initial definition of clinical success (GCSI improvement >0.6), in ITT analysis, the clinical efficacy rate was 70% in the G-POEM group versus 40% in the BTI group (95%CI -0.11 to 0.52;  $P=0.05$ ).

#### Clinical efficacy at 1 year

At 12 months, the clinical efficacy rate (GCSI decreasing >1) in ITT analysis, the rate was 60% in the G-POEM group vs. 40% in the BTI group (95%CI -0.30 to 0.40;  $P=0.20$ ).

The delta between GCSI at inclusion and at 12 months was 1.2 (SD 1.1) in the G-POEM group and 0.9 (SD 1.1) in the BTI





► **Table 3** Main results in terms of efficacy at 3 months, with both definitions, and 12 months on intention-to-treat analysis.

|  | G-POEM      | BTI        | P value |
|--|-------------|------------|---------|
| 3-month clinical success rate                      | 65% (13/20) | 40% (8/20) | 0.10    |
| GCSI mean change at month 3, mean (SD)             | 1.5 (1.2)   | 1.2 (1.2)  | 0.32    |
| 3-month clinical success rate (GCSI decrease >0.6) | 70% (14/20) | 40% (8/20) | 0.05    |
| 12-month clinical success rate                     | 60% (12/20) | 40% (8/20) | 0.20    |
| GCSI mean change at month 12, mean (SD)            | 1.2 (1.1)   | 0.9 (1.1)  | 0.62    |

G-POEM, gastric peroral endoscopic myotomy; BTI, botulinum toxin injection; GCSI, Gastroparesis Cardinal Symptom Index.

group ( $P=0.62$ ). Both groups showed improvement in the GCSI scores at 3 and 12 months.

Finally, the two groups were comparable with regard to the evolution of the GCSI subscores at both 3 months and 12 months (► **Table 4**).

### Quality of life

At 3 months, responses to the SF-12 and GIQLI questionnaires were received from all patients in the G-POEM group and 17 in the BTI group; at 1 year, there were 4 and 3 responses, respectively. For the SF-12 score, no difference was demonstrated at 12 months, with mean scores of 37.9 (SD 4.0) in the G-POEM group versus 39.2 (SD 3.6) in the BTI group ( $P=0.38$ ).

For the GIQLI score, we found an improvement in the scores of both groups at 3 months, with a mean score of 78.2 (SD

29.1) in the G-POEM group ( $n=20$ ) and a mean score of 79.6 (SD 32.3) in the BTI group ( $n=17$ ), with no difference between the two groups ( $P=0.89$ ).

### GES evolution

The GES findings, including the mean half-emptying time and solid residual activity at 2 and 4 hours, were comparable between the two groups at baseline. At 3 months, 72% of the patients in the G-POEM group ( $n=13/18$ ) had an improved GES compared with 50% in the BTI group ( $n=9/18$ ;  $P=0.17$ ). However, there was no difference between the two groups in any of the GES findings at 3 months (**Table 1s**).

### Adverse events

We report no AEs in the BTI group and only one intraoperative AE in the G-POEM group (5%;  $P=0.13$ ). This was a patient who had an intraoperative mucosotomy on the duodenal side, which was managed per-operatively by clipping, without any clinical manifestation; it was classified as grade 1 in the AGREE classification.

During follow-up, two minor postoperative AEs occurred in the G-POEM group (10%), both classified AGREE grade 1. One patient presented with epigastric pain, without any sign of severity or peritonitis, and required an additional 24 hour of hospitalization for analgesia. The second patient presented with fever and abdominal pain on postoperative day 2. A computed tomography scan showed pyloric edema without perforation. The evolution was favorable, with the patient receiving oral antibiotic therapy and being discharged within 5 days.

### Discussion

We present here the first double-blind controlled randomized study comparing G-POEM versus BTI in the treatment of refractory gastroparesis. The primary outcome was the 3-month clinical efficacy because, when the study was designed, G-POEM was emerging, with only a few studies and short-term efficacy evaluations [19, 21, 24, 35, 36]. Since that time, several series have been published, with up to 1 year of follow-up, demonstrating an efficacy rate between 60% and 65% [25, 31, 37]. The definition of efficacy also changed over the years, with GCSI improvement changing from 0.6 to 1, in order to improve the selection of patients and not treat patients with dyspepsia. In the two more recent studies, definitions were at least a GCSI decrease of >1, and even a decrease of 25% in two subscores [28, 29].

Regarding the methodology, all our included patients had confirmed delayed gastric emptying, using the recommended technique for GES. In addition, the randomized double-blind design was particularly important to us to assess the effect of a treatment on a functional disease.

The choice of comparing G-POEM with BTI, instead of with a placebo was made for ethical reasons. We acknowledge that not including a sham arm could appear as a methodological limitation; however the ethical committee who examined the protocol did not allow us to propose sham procedures in patients suffering from severe and refractory pathology. Another

► **Table 4** Main evolution in all GCSI subscales for the two groups at 3 months and 12 months.

|                                    | Month 3          |                  |             | Month 12         |                  |             |
|------------------------------------|------------------|------------------|-------------|------------------|------------------|-------------|
|                                    | G-POEM           | BTI              | P value     | G-POEM           | BTI              | P value     |
| Nausea                             | 2.0 (1.6)        | 1.9 (1.7)        | 0.87        | 2.3 (1.8)        | 2.1 (1.2)        | 0.83        |
| Retching                           | 1.6 (1.5)        | 1.6 (1.7)        | 0.89        | 1.4 (1.4)        | 1.7 (1.5)        | 0.49        |
| Vomiting                           | 1.3 (1.7)        | 0.9 (1.6)        | 0.49        | 1.4 (1.7)        | 1.4 (1.6)        | 0.92        |
| Vomiting subscale                  | 1.6 (1.4)        | 1.5 (1.4)        | 0.93        | 1.8 (1.5)        | 1.9 (1.2)        | 0.69        |
| ▪ Early satiety                    | 2.2 (1.5)        | 2.4 (1.8)        | 0.70        | 2.8 (1.9)        | 3.0 (1.7)        | 0.85        |
| ▪ Not able to finish a normal meal | 2.4 (1.8)        | 2.2 (2.0)        | 0.76        | 2.4 (2.0)        | 2.2 (2.0)        | 0.71        |
| ▪ Post-prandial fullness           | 2.8 (1.7)        | 2.7 (1.8)        | 0.87        | 3.0 (1.8)        | 3.1 (1.7)        | 0.98        |
| ▪ Loss of appetite                 | 1.8 (1.6)        | 1.4 (1.7)        | 0.31        | 2.1 (2.0)        | 1.9 (1.8)        | 0.71        |
| Satiety subscale                   | 2.4 (1.4)        | 2.2 (1.5)        | 0.81        | 2.7 (1.5)        | 2.7 (1.4)        | 0.84        |
| ▪ Bloating                         | 2.6 (1.8)        | 2.4 (2.1)        | 0.90        | 3.1 (1.8)        | 2.7 (1.7)        | 0.56        |
| ▪ Stomach/belly visibly larger     | 2.4 (1.8)        | 2.3 (2.0)        | 0.92        | 2.9 (1.8)        | 2.4 (1.9)        | 0.41        |
| Bloating subscale                  | 2.5 (1.7)        | 2.4 (1.9)        | 0.96        | 3.1 (1.6)        | 2.7 (1.7)        | 0.52        |
| <b>Total GCSI score</b>            | <b>2.2 (1.4)</b> | <b>2.1 (1.3)</b> | <b>0.87</b> | <b>2.5 (1.4)</b> | <b>2.4 (1.1)</b> | <b>0.89</b> |

GCSI, Gastroparesis Cardinal Symptom Index; G-POEM, gastric peroral endoscopic myotomy; BTI, botulinum toxin injection. All values are given as mean (SD).

limitation could be the loss of patients to follow-up, especially in the botulinum toxin group. One explanation could be that the procedure was just starting to be used and we included some patients coming from other regions who then stopped coming, particularly if the procedure failed; however, the ITT analysis should offset this issue. As for the quality-of-life scores at 1 year, the missing data were because the questionnaires were autofilled by the patients, who did not bring them to the visits.

Despite this, our population was representative of the gastroparesis population, with the three main etiologies represented and no difference between the groups [14]. Therefore, as a main outcome, it is important to underline that our study allowed us to prospectively confirm the results published in the literature. Indeed, the efficacy rate of G-POEM at 1 year was 60%, with no severe AEs (AGREE  $\geq 3$ ) and a low overall AE rate, demonstrating the interesting benefit-to-risk ratio of the procedure. This outcome is slightly lower than was seen in the study of Martinek et al., but is probably related to the lower proportion of diabetic patients, in whom we currently know the procedure is more effective [28,29]; however, we included about the same number of patients.

In the ITT analysis at 1 year, and assuming that patients lost to follow-up were failures, the efficacy rate was 60% for G-POEM versus 40% in the BTI group. Although the data analysis could not demonstrate a statistical difference, the difference of 20 percentage points is clinically relevant and confirms our impression in clinical practice.

The lack of significance could be due to the sample size calculation, which was based on the literature data from 2016 [38], where the patients in the BTI group reached an efficacy rate of 40% and G-POEM 80% at 3 months. We may hypothesize

that our sample size was insufficient to have enough power to demonstrate any potential difference; however, it was comparable with the number of patients included in the randomized study of G-POEM versus sham performed by Martinek et al. [29]. It could also be that the sample sizes were insufficient in the two previous randomized studies of BTI, plus the BTI dose was 100 IU instead of the 200 IU used in our study, which may explain the disappointing results of BTI compared with the open-label studies. Another reason may be that there were more cases of diabetic gastroparesis and fewer idiopathic cases in the BTI group than in the G-POEM group (**Table 2s**). The last hypothesis is that there was a major placebo effect. Indeed, in functional diseases, the frequency of the follow-up and the availability of the medical team for patients, even in the placebo groups, increases efficacy. In our study, patients were seen five times in clinics appointments over the year following the procedure, which could have improved the placebo effect.

In terms of the GES findings, the same statement could be made, as no difference was observed based on our data at 3 months. This could be explained by the lack of power, as well as the precocity of the GES examination and the sensitivity of this examination [5,39]. One disappointment was with regard to the quality-of-life assessment, which was supposed to be provided by the patients (self-questionnaires), for which there is a lack of interpretable data.

In conclusion, our results suggest that G-POEM reaches an efficacy rate at 60% at 1 year, confirming other data in the literature. A difference in efficacy with BTI could not be statistically confirmed, but may be clinically relevant. Moreover, this study confirms the interest in treatments targeting the pylorus,

either mechanically or chemically, in the treatment of refractory gastroparesis.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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## Clinical Trial

Trial Registration: ClinicalTrials.gov | Registration number (trial ID): NCT02927886 | Type of study: respective randomized bicenter study

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