Discussion Summary

G-POEM for severe and refractory gastroparesis

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Abstract

Gastroparesis is characterized by nausea, vomiting, abdominal pain and delayed gastric emptying. This chronic condition has few effective medical options. Gastric peroral endoscopic myotomy (G-POEM) is an emerging alternative to surgical pyloroplasty or pyloromyotomy that may provide relief in carefully selected patients with severe symptoms. This article summarizes the @GIJournal Twitter discussion of Martinek et al, “Endoscopic pyloromyotomy for the treatment of severe and refractory gastroparesis: a pilot, randomised, sham-controlled trial,” originally published in Gut. In this study of 40 patients, G-POEM was associated with significant improvement in symptoms and quality of life at 6 months, including patients who crossed over from sham, and especially in those with diabetic gastroparesis. Future studies will provide data on longer follow-up periods and examine strategies for G-POEM candidate selection.
Introduction

Gastroparesis is a chronic condition characterized by nausea, vomiting, satiety, and abdominal pain, and evidence of delayed gastric emptying in the absence of mechanical obstruction, most often with 4-hour gastric emptying scintigraphy. The 2022 American College of Gastroenterology (ACG) guidelines on gastroparesis recommend dietary modification (low-residue food, small frequent meals) and medical therapy, and reserve non-pharmacologic therapy for patients with refractory symptoms. (1) Gastric peroral endoscopic myotomy (G-POEM) is a minimally invasive technique thought to address pylorospasm and has been reported to be safe and associated with symptom improvement in gastroparesis. (2–4) The ACG guidelines make a conditional recommendation for consideration in patients with refractory symptoms and note a low quality of evidence. (1)

The current study by Martinek et al (2022) (5) is a trial of G-POEM in the Czech Republic and Slovakia and is the first to incorporate a sham arm with crossover in severe and refractory gastroparesis. Patients were assessed with EGD, scintigraphy, and symptom and quality of life questionnaires at 3, 6, and 12 months. The trial was stopped early (interim analysis at 40%) due to a significant primary difference between G-POEM and sham arms. G-POEM was associated with a significantly higher odds of treatment success (≥50% symptom improvement at 6 months), with an OR=9.0 (95% CI 2.0–40.2, p=0.005) compared to sham. Of the sham patients who were offered crossover G-POEM, 9/12 (75%) patients had subsequent treatment success. The procedure was considered safe, with 3 serious events related to G-POEM (ulcer, mucosal perforation, dumping syndrome); 1 G-POEM could not be completed due to submucosal fibrosis.
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Figure 1: Twitter summary slides

Introduction

- Many patients have persistent and debilitating symptoms of gastroparesis despite current treatment options
- Spastic pyloric muscle has been proposed as a pathophysiologic mechanism in gastroparesis
- There is a lack of evidence for other pylorus-directed therapies (pyloroplasty, Botox, balloon dilatation)
- However, endoscopic pyloromyoplasty (G-POEM) seems promising based on prior non-randomized, non-controlled trials
- This is a randomized, sham-controlled trial of G-POEM for severe and refractory gastroparesis conducted at two European centers

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<thead>
<tr>
<th>G-POEM (n=21)</th>
<th>Sham (n=19)</th>
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<tbody>
<tr>
<td><strong>Baseline</strong> EGG, scintigraphy or breath test, questionnaire (GCSI, PGI-SYM, PGI-QOL)</td>
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<td>G-POEM procedure</td>
<td><strong>G-POEM procedure</strong></td>
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<tr>
<td>1. Submucosal injection and mucosal incision 4-5 cm proximal to the pyloric channel</td>
<td><strong>Sham</strong> EGG under general anesthesia 34-40 mins Normotensive</td>
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<td>2. Creation of submucosal tunnel towards a pyloric ring</td>
<td><strong>Sham</strong> EGG under general anesthesia 34-40 mins Normotensive</td>
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<td>3. Closure with endoscopic suturing or clips</td>
<td><strong>Sham</strong> EGG under general anesthesia 34-40 mins Normotensive</td>
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<tr>
<td>4. Post procedure PO PH phase I and II following</td>
<td><strong>Sham</strong> EGG under general anesthesia 34-40 mins Normotensive</td>
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<td><strong>2 month follow up:</strong> EGG, scintigraphy, questionnaires</td>
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<td><strong>6 month follow up:</strong> EGG, questionnaires</td>
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Patient selection and characteristics

- Adults with severe (GCSI > 23) and refractory (> 6 months) gastroparesis from any etiology
- Had to have tried at least 1 prokinetic
- No opioids within 12 months
- No uncontrolled diabetes, uncontrolled constipation, eating disorders, other conditions. No major esophageal or gastric surgery (fundoplication or Heller myotomy) or previous pyloroplasty or pyloromyotomy
- G-POEM and sham groups had similar proportions of diabetic (~40%), post-surgical (~30%), and idiopathic (~25-30%) gastroparesis. 35% had recurrent hospitalizations for gastroparesis.

Outcomes

- **Primary outcome:** Proportion of patients with “treatment success” (≥50% symptom decrease at 6 months in intention-to-treat cohort) after G-POEM
  - 15/21 (71%, 95% CI 59-86%) success in G-POEM group, 4/20 (20%, 95% CI 6-47%) success in sham group
  - OR=9.0 (95% CI 2.0-40.2, p=0.003) success with G-POEM
- Rate of success higher in diabetic gastroparesis. Gastric emptying and EndoFLIP did not significant predictors of success
- Secondary outcomes:
  - G-POEM and crossover treatment showed improvement in GCSI, PGI-SYM, PGI-QOL, gastric emptying rates on scintigraphy
  - 3 adverse events related to G-POEM; 1 G-POEM could not be completed due to submucosal fibrosis

Discussion

This article summarizes the June 5, 2022 @GIJournal Twitter discussion of the study, including a lightly edited transcript of discussant and audience questions with answers from a content expert (AA), moderators (SA, SM), and trainee discussant (JL).

AA: Very impressive results favoring G-POEM. I found the crossover results after randomization especially impressive. What stands out to others?
SM: Crossover results and the OR 9.0 for success are very impressive. Is there a difference in technique here? Double myotomy?

@GIJournal Volume 2, Issue 21, August 2022
@ijlalakbar: many studies on G-POEM show initial success but I have noted data show the effect isn’t as long-lasting as EPOEM [for achalasia].

AA: This is a big point we haven’t covered yet. This study was ended early by the safety monitoring board due to safety concerns of using general anesthesia in sham patients. Other studies have shown a drop-off in efficacy over time. Follow-up period was 6 months.

JL: Authors mention data collection up to 36 months so hopefully can evaluate for regression to the mean in this refractory population. [This is] potentially an issue for gastric stimulators.(6)

@DrSaeed: recurrence could be from incomplete myotomy and regaining pyloric tone after healing. EndoFLIP can help once we establish the numbers associated with good response.

AA: Another area where we need standardization of protocol and normal values.

Q1. This randomized, sham-controlled trial showed significant treatment response for G-POEM vs sham (71% vs 21%, p<0.05) to the point that it was stopped early. Is this the evidence we need to offer G-POEM as first line for carefully selected patients?

AA: Short answer is yes with a few caveats. This is an extremely well-done study with sham group and crossover design.

@DrSaeed: This is proof that it works in carefully selected patients. Should be offered as a management option in gastroparesis.

AA: Yes, this is one of the key takeaway points: patient selection. Many patients we see to consider G-POEM have not been tried on prokinetic agents. Patients should be refractory to medical management and lifestyle changes.

SM: This data is great. Too good to be true? I don’t think retrospective data has been this promising in the USA.

SA: I think it’s in line with what other studies have shown, 70% response rate is typical. Hopefully the rigor and methodology here will convince people of the utility of G-POEM.

@AllonKahn: Who do you think needs the most convincing? I hope we can all agree the current [standard of care] has disappointing efficacy. Are interventional folks reluctant? Referring GIs? All the above?

SA: Interventional folks are very much on board. I think a lot of the hesitancy right now is whether patients should go straight to G-POEM or try other pyloric-directed therapies like stents or Botox first.

AA: Yes, agreed. Let’s not forget though that 2 prior sham-controlled trials have not shown benefit of intrapyloric Botox.

@AllonKahn: Yes, in my experience I have found [Botox] to be disappointing. Also have to warn patients that cost/coverage may be an issue.

AA: There is the risk of [Botox causing] submucosal fibrosis, making future G-POEM difficult. In my opinion, in the absence of data to support Botox, I recommend against it.

SA: I hate fibrosis at the pylorus! Say no to Botox.

AA: Sometimes we don’t even realize the fibrosis has occurred, which can force the tunnel to go off center and you can get lost.
Q2. This trial selected patients with severe (GCSI >2.3) and refractory (>6 months) gastroparesis from any etiology for G-POEM. Is this similar to your selection criteria? Who is the ideal candidate for G-POEM?

AA: Million-dollar question. We try to exhaust medical options, ensure an accurate diagnosis, rule out gastroparesis-like syndromes such as functional dyspepsia and counsel patients on existing data, so this article is a big help. I have always found it quite interesting that it is patients with more severe symptoms that benefit from G-POEM as illustrated in other studies and confirmed in this sham RCT.

JL: How do you consider chance of success for G-POEM if patient has or has not responded to Botox before?

@DrSaeed: I offer my patients a temporary trial of Botox that can help decide if the G-POEM will work or go directly to G-POEM discussing risks and benefits. I find [many patients] decide to go directly to G-POEM. I completely agree with [selecting for severe and refractory symptoms] Control diabetes, constipation, stop opiates prior to offering G-POEM.

SA: Good point. Very important to control diabetes, stop opiates, and counsel patients that pain-predominant symptoms may not improve.

@ChrisAndersonM4: They didn’t include patients on opioids in the last 12 months. That seems to be a tough one here in the US.

Q3. Some advocate for trans-pyloric stenting or Botox as a first step before G-POEM to see if pylorospasm is a dominant driver of disease. In light of this trial, is this still necessary? Or can we go straight to G-POEM?

AA: I recommend no Botox. We have a sham RCT on transpyloric stent ongoing.(7) SM: Attended a lecture by @qcai at DDW 2022; his approach was that even if G-POEM doesn’t work, it’s such a low-risk procedure that it’s worth attempting early.

AA: Interesting thought. One of the main reasons I defer until later is that [there are] not a lot of management options after G-POEM.

@AntoineDebourd1: I think that one of the main side effects of G-POEM is to exclude potential candidates for other trials…I use it carefully in young candidates. The other opinion I have, which has not been demonstrated in the literature, is to be wary of very constipated patients in whom it is rarely a success. With regards to Botox injection in the pylorus, I would reason as I would for achalasia: good responders to G-POEM will also have a good short-term response to Botox. This was shown in a French RCT that will be published soon. Since the morbidity of Botox and G-POEM are not hugely different, I would go directly to G-POEM to avoid having to redo an endoscopy.

SA: Great point @AntoineDebourd1! Patients with pan-GI dysmotility just don’t do well. I wonder if we should start incorporating a comprehensive motility eval with SmartPill, for example, into our selection algorithm.

JL: @dbrennerGIMD’s motto is that evaluating the role of constipation and the often-overlooked pelvic floor/dyssynergia is critical in these patients. There is a long way to go for medical options as domperidone not readily available in the US and everything besides metoclopramide is technically off-label.

AA: The challenges of medical therapy summarized well.
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@AllonKahn: Totally agree with you both. Isolating a complex set of symptoms to the pylorus in this setting is illogical. With better prokinetics like prucalopride that may address both issues, we may be better off with medical/lifestyle management.

@AntoineDebourd1: Prucalopride is also a constipation treatment!

Q4. This trial showed an increased efficacy for G-POEM in diabetic gastroparesis compared to idiopathic or post-surgical (though it was not powered to detect difference based on etiology). Is this similar to your real-life experience?
SM: Saw a couple of posters at DDW 2022 showing a good response to Botox in past lung transplant patients. What are your thoughts?
AA: This is one patient population in which I’m willing to incorporate G-POEM early because aspiration can really affect graft function. We have had success working with @NM_Lung offering G-POEM in lung transplant recipients.

Q5. What is your technical approach to G-POEM? This trial used a greater curve approach with a single myotomy though some now advocate for lesser curve approach or double myotomy. What works best?
AA: I still use greater curve with a single myotomy—I try to make it wide like a double myotomy. Going forward I will be doing double myotomy. I don’t think there is really a difference between lesser curve or greater curve, like anterior versus posterior for EPOEM.
SA: Me, too. Haven’t made the switch to double but probably coming. Those who do lesser curve swear by it. Surgeons seem to like it. Pop in right above pylorus and procedure done in 15 minutes. No getting lost.
@neilRsharmaMD: Same as trial—but using a wide single incision. Will need to see how time and or outcome changes with lesser curve.

Q6. Does this trial change the way you will counsel patients before and after G-POEM? Are there certain symptoms that tend to respond better than others, i.e., nausea or bloating versus pain?
AA: Absolutely. Patients understand placebo results when you compare [this study] to COVID vaccine trials. Patients with pain only are not candidates for G-POEM in my opinion. They should have nausea or bloating at a minimum, and if vomiting, even better candidates.
SM: I would be reluctant to send patients with pain-predominant symptoms. Most patients have been on chronic or intermittent narcotics, too. However, this seems to be a great option for our nausea/vomiting patients.
@RobertBechara: Agree. It helps in counseling patients—including those not candidates for G-POEM. Counseling the patient why they are NOT going for G-POEM can also be a challenge, and good data is helpful for that discussion.

@tberzin: My practice has been to consider deferring G-POEM if the pylorus is “widely patent” at time of procedure, since it’s hard for me to fathom that making it more open will actually help, although I understand pylorus physiology is dynamic—what do others do?
@ijlalakbar: This is also the practice of [Dr. Martinek, lead study author].
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@DrSaeed: I personally don’t rely on presence of pylorospasm during endoscopy. Like you said, it’s dynamic. The fact that it’s open during endoscopy doesn’t mean it’s paralyzed. The study discussed today showed good response without ruling out those patients.
@krishnanendo: I try to risk stratify with pyloric EndoFLIP. There is reasonable normative data on what counts as pylorospasm. Further, the data with both G-POEM and Botox suggests we can select responders better by using EndoFLIP.
SA: Agree with both @DrSaeed and @krishnanendo. At present I still proceed with G-POEM but I should look back to see if there has been a different response rate based on my subjective evaluation of pyloric patency. This is probably a gray area where EndoFLIP could help!

Conclusion
This randomized pilot study of G-POEM with sham crossover is the first to provide evidence that G-POEM is superior to sham, with significant improvements in symptoms, quality of life, and metrics including gastric emptying and pyloric distensibility (although improvement in these measures alone were not associated with symptom improvement). Work to provide data on follow-up times up to 36 months post-procedure is ongoing. Results need to be stratified by other causes of gastroparesis such as postsurgical(8) and idiopathic gastroparesis. Strategies to optimize patient selection for G-POEM must be developed. In the @GIJournal discussion, discussants recommended against repeated use of Botox given the risk of submucosal fibrosis and G-POEM for pain-predominant symptoms, discussed the possible role of pyloric EndoFLIP, and the value of this study’s methodology with placebo. Discussants agreed that patient selection for G-POEM is critical to improving rates of success. Patients should have failed a prokinetic trial, be concurrently evaluated for other GI dysmotility, and be treated for comorbidities like constipation. In summary, although more data is needed, G-POEM appears to be a promising treatment option for patients with severe and refractory gastroparesis symptoms, particularly nausea and vomiting.

References


