



## Innovative gastric endoscopic muscle biopsy to identify all cell types, including myenteric neurons and interstitial cells of Cajal in patients with idiopathic gastroparesis: a feasibility study (with video)

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**Background and Aims:** The pathophysiology of some GI neuromuscular diseases remains largely unknown. This is in part due to the inability to obtain ample deep gastric wall biopsies that include the intermuscular layer of the muscularis propria (MP) to evaluate the enteric nervous system, interstitial cells of Cajal (ICCs), and related cells. We report on a novel technique for gastric endoscopic muscle biopsy (gEMB).

**Methods:** Patients with idiopathic gastroparesis were prospectively enrolled in a feasibility study by using a novel “no hole” gEMB. Main outcome measures were technical success, adverse events, and histologic confirmation of the intermuscular layer, including myenteric neurons and ICC. The gEMB was a double resection clip-assist technique. A site was identified on the anterior wall of the gastric body as recommended by the International Working Group on histologic techniques. EMR was performed to unroof and expose the underlying MP. The exposed MP was then retracted into the cap of an over-the-scope clip. The clip was deployed, and the pseudopolyp of MP created was resected. This resulted in a no-hole gEMB.

**Results:** Three patients with idiopathic gastroparesis underwent gEMB. Patients had severe delayed gastric emptying with a mean ( $\pm$  standard deviation [SD]) of  $49 \pm 16.8\%$  of retained gastric contents at 4 hours. They had no history of gastric or small-bowel surgery and did not use steroids or other immunosuppressive drugs. The gEMB procedure was successfully performed, with no procedural adverse events. Postprocedural abdominal pain was controlled with nonsteroidal anti-inflammatory agents and opioid analgesics. Mean length of resected MP was  $10.3 \pm 1.5$  mm. Mean procedure time was  $25.7 \pm 6$  minutes. Hematoxylin and eosin (H&E) staining of tissue samples confirmed the presence of both inner circular and outer longitudinal muscle, as well as the intermuscular layer. H&E staining showed reduced myenteric ganglia in 1 patient. In 2 patients, specialized immunohistochemistry was performed, which showed a marked decrease in myenteric neurons as delineated by an antibody to protein gene product 9.5 and a severe decrease in ICC levels across the muscle layers. At 1 month follow-up, upper endoscopy showed a well-healed scar in 2 patients and minimal ulceration with a retained clip in 1 patient. CT of the abdomen confirmed the integrity of the gastric wall in all patients. Because of lack of an immune infiltrate in the resected samples, patients were not considered suitable for immunosuppressive or steroid therapy.

**Conclusions:** gEMB is feasible and easy to perform, with acquisition of tissue close to surgical samples to identify myenteric ganglia, ICCs, and multiple cell types. The ability to perform gEMB represents a paradigm shift in endoscopic tissue diagnosis of gastric neuromuscular pathologies.

(footnotes appear on last page of article)



This video can be viewed directly from the GIE website or by using the QR code and your mobile device. Download a free QR code scanner by searching “QR Scanner” in your mobile device’s app store.

The pathophysiology of many GI neuromuscular diseases, including idiopathic gastroparesis and functional dyspepsia, is not well understood.<sup>1,2</sup> There is growing evidence to support an underlying heterogeneous neuromuscular pathology in patients with gastroparesis and emerging evidence for cellular changes in functional diseases such as functional dyspepsia.<sup>3-5</sup> Endoscopic

mucosal-based biopsies do not allow for evaluation of the myenteric plexus or interstitial cells of Cajal (ICC) networks that lie within the muscularis propria (MP) or the intermuscular layer of the MP. Currently, we rely on surgical approaches such as laparoscopic wedge biopsy to obtain sufficient tissue samples of the gastric wall.

A readily available, effective, and safe endoscopic technique that enables ample deep gastric wall biopsies to include the intermuscular layer of the MP for evaluation of the enteric nervous system, immune cells, and ICCs may provide invaluable insights into the pathogenesis of these disorders. The aims of this study were to (1) determine the efficacy of an innovative gastric endoscopic muscle biopsy (gEMB) technique; (2) identify the muscle layers included in the resected specimen and the presence of myenteric ganglia and ICCs; (3) determine the procedural and long-term safety of the technique; and (4) identify neuromuscular pathologic changes in patients with idiopathic gastroparesis.

## METHODS

### Patients

Patients were prospectively enrolled in this feasibility study approved by the Institutional Review Board. Patients diagnosed with symptomatic refractory idiopathic gastroparesis were recruited. Only patients with documentation within the previous 2 years of delayed gastric emptying with >30% retained gastric contents at 4 hours, based on 296 kcal of a solid-liquid, fat-containing standard meal gastric emptying test, were included. Patients were excluded if there was a history of oropharyngeal, esophageal, gastric, or small-bowel surgery, esophageal stricture, abdominal radiation therapy, percutaneous endoscopic gastrostomy or jejunostomy, coagulopathy, and use of steroids or immunosuppressive drugs.

Patients were admitted after the procedure for 24-hour observation. Patients were maintained on clear liquids on day 1 of the procedure, and the diet was advanced as tolerated thereafter. Omeprazole 40 mg twice daily orally for 4 weeks and perioperative antibiotics were administered. Patients were contacted by telephone 48 hours and 1 week after the procedure. At 1-month follow-up, upper endoscopy was repeated to review the mucosal aspect of the resection site, and an abdominal CT was performed to assess the integrity of the resection site.

### Description of the technique

gEMB involves a double resection clip-assist technique. A site was identified along the anterior wall of the gastric body, midway between the greater and lesser curves, as recommended by the International Working Group on histologic techniques, which is a consensus document by

expert neurogastroenterologists.<sup>6</sup> From an endoscopic perspective, the anterior wall is ideal both from safety (avoiding the gastroepiploic and gastric vessels) and ease of procedure performance perspectives. EMR by using the band ligation approach (Duette; Cook Endoscopy, Bloomington, Ind) was initially performed to unroof and expose the underlying MP. An over-the-scope clip (Padlock Clip, 11 mm; Aponos, Kingston, NH) was fitted on a diagnostic upper endoscope (GIF-180; Olympus America, Center Valley, Pa) and advanced to the exposed MP. A tri-pronged tissue retraction device (OTSC Anchor; Ovesco Endoscopy, Tübingen, Germany) was passed through the working channel of the endoscope and deployed through the MP, which was then retracted and suctioned into the cap of the clip. Once an adequate amount of tissue was entrapped within the cap, the clip was deployed. The created pseudopolyp of MP was resected by using a hot snare (Acusnare; Cook Endoscopy). Resection was done approximately 5 mm above the deployed clip to ensure that ample tissue remained for a secure closure. This approach resulted in a “no-hole” gEMB. Effective closure of the biopsy site was confirmed during endoscopy by visible closure without disruption, sustained distension of the gastric lumen with insufflation of CO<sub>2</sub>, and absence of radiopaque contrast material leakage into the peritoneal cavity after intragastric injection determined fluoroscopically. The resected specimens of MP as well as mucosa and submucosa from the EMR were retrieved, pinned, measured, and submitted for histology (Video 1, available online at [www.giejournal.org](http://www.giejournal.org)).

## RESULTS

We report on 3 female patients with a mean age of 33 ± 8.5 years with symptomatic refractory idiopathic gastroparesis who underwent gEMB. Predominant symptoms were nausea, vomiting, abdominal pain, and weight loss that were ongoing for several years. Severe delayed gastric emptying with a mean (± SD) of 49% ± 16.8% of retained gastric contents at 4 hours based on a 296 kcal solid-liquid, fat-containing standard meal gastric emptying test was documented in study patients. A double resection clip-assist gEMB was performed successfully in all patients (Fig. 1A and B). There were no intraprocedural adverse events. The mean (± SD) size of resected MP was 10.3 ± 1.5 mm (Fig. 2). The mean size of resected mucosa and submucosa was 22 ± 6.1 mm. Mean (± SD) procedure time from endoscope intubation to retrieval of tissue specimens was 25.7 ± 6 minutes.

Tissue samples on hematoxylin and eosin (H&E) staining confirmed the presence of MP with inner circular and outer longitudinal muscle as well as an intermuscular layer in all patients (Fig. 3). Abnormalities were noted in 2 of 3 patients (66%). H&E staining showed reduced myenteric ganglia in 1 patient. In 2 of the 3 patients, additional

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