Title: IMPLEMENTATION OF A PERORAL ENDOSCOPIC MYOTOMY PROGRAM

Authors: Pablo Miranda-García, Raquel Muñoz González, José Carlos Marín Gabriel, Eduardo Albéniz, Sergio Casabona Francés, Teresa Pérez Fernández, Montserrat Grau, Cecilio Santander Vaquero

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Implementation of a peroral endoscopic myotomy program

Pablo Miranda-García1,2, Raquel Muñoz González1, José Carlos Marín Gabriel3, Eduardo Albéniz4, Sergio Casabona Francés1,2, Teresa Pérez Fernandez1, Montserrat Grau5 and Cecilio Santander Vaquero1,2


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Correspondence: Pablo Miranda García. Gastroenterology Department. Hospital Universitario de La Princesa. C/ de Diego de León, 62. 28006 Madrid, Spain
e-mail: pmpablomiranda@gmail.com

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ABSTRACT

Introduction: the aim of our study was to develop a peroral endoscopic myotomy (POEM) program in our Unit following a two-step sequence: training on animal models and supervision by an experienced endoscopist during the first human cases.

Methods: a single endoscopist experienced in advanced endoscopy was trained in POEM. After observing POEM in referral centers, training was implemented on swine
models (preclinical phase). Technical aspects and adverse events were prospectively recorded. A first subset of cases (group A) was compared to a second one (group B) to assess our progression. Finally, POEM was implemented in humans under the supervision of an experienced endoscopist (clinical phase). The outcomes and adverse events were prospectively recorded.

**Results:** during the preclinical phase, 15 POEM procedures were performed on live pigs. Severe adverse events (AE) were less frequent in group B than in group A (12 % vs 57 %, p = 0.07). After nine cases, a plateau of adverse events was reached. During the clinical phase, eleven POEM procedures were performed in patients under expert supervision. Technical and clinical (Eckardt score ≤ 3) success were 100 % and 91 %, respectively (follow-up 3-21 months). In two cases, intervention of an experienced endoscopist was required (cases 2 and 3) because of a difficult orientation at the esophagogastric junction. One mild pneumoperitoneum occurred, with no severe adverse events reported.

**Conclusions:** training in animal models and supervision by an experienced endoscopist during the first cases could provide the necessary skills to perform POEM safely and effectively.

**Keywords:** Esophageal achalasia. Myotomy. Education. Learning curve. Animal models.

**INTRODUCTION**

Since its initial development (1,2), peroral endoscopic myotomy (POEM) has become a first line treatment for achalasia (3-5). It is based on the creation of a submucosal tunnel using submucosal dissection (ESD) techniques to gain access to the muscularis propria. POEM is considered to be a challenging technique, which demands an extensive expertise in ESD and advanced endoscopy. Japanese guidelines suggest that endoscopists should have performed more than 20 esophageal ESD before they start POEM (6). Even in experienced hands, wide variations in the POEM learning curve have been reported, from seven to more than 40 (7-9). Esophageal ESD is less frequently performed in western countries than in Asia, and a training program on an animal model could be a good way to become skilled in POEM, even with limited experience.
in esophageal ESD.
The aim of our study was to develop a POEM program in our Unit, following a training sequence based on animal training and supervision by an experienced endoscopist.

**METHODS**
A prospective training program was performed from March 2017 to June 2018. All procedures were performed according to the national regulations under the supervision of a veterinary at the Animal Facility and Experimental Surgery Unit of our center. Live swine models were used and the ethical committee approved the study on 13th September 2016 (IRB code 100920167416).
Once the training program on animals was completed, POEM was performed under the supervision of an experienced endoscopist in POEM in the first human cases. Informed consent was obtained in all cases.

A single endoscopist (PMG) trained in advanced endoscopy including endoscopic ultrasound, endoscopic retrograde cholangiopancreatography and wide field endoscopic mucosal resection performed all the procedures. As an observer, he attended more than 15 POEM procedures at expert centers (Hôpital Nord, Marseille, France; Showa University Hospital, Tokyo, Japan). However, he had limited experience in ESD, with more than 50 cases of ESD in animal models and five rectal cases, but no esophageal ESD experience in the clinical practice.

**Preclinical phase**

**Equipment**
A Fujifilm forward viewing EG-530WR endoscope (Fujifilm, Tokyo, Japan) was used. Air insufflation was used as CO₂ was not available. An ST Hood DH-28GR (Fujifilm, Tokyo, Japan) cap was attached to the tip of the endoscope. The ICC200 ERBE electrosurgical generator was used (ERBE, Tübingen, Germany). An injection needle model Interject 23 g (Boston Scientific, Natick, MA, USA) was used for the first bleb and the Waterfall irrigation pump (EMED, Opacz Kolonia, Poland) helped with injection during tunneling. The procedures were performed with a Triangle Tip Knife Jet (Olympus, Tokyo, Japan) or a Flush Knife BT 2.0 (Fujifilm, Tokyo, Japan). Coagrasper® hemostatic forceps
(Olympus, Tokyo, Japan) were used for the coagulation of vessels. Resolution360™ clips (Boston Scientific, Natick, MA, United States) were applied to close the entry site.

**POEM technique**
All procedures were performed under general anesthesia. All POEM procedures were performed according to the standard technique.
Mucosal entry: the site was chosen 10-15 cm proximal to the esophagogastric junction (EGJ), using the 5 o'clock approach. A saline solution mixed with indigo carmine was injected to create a bleb. Then, a 2-3 cm longitudinal incision of the mucosa was made (ENDO CUT® 80W Effect 2).
Submucosal tunneling: a technique similar to ESD was followed to create a tunnel from the esophagus to 2-3 cm beyond the EGJ (Forced Coagulation 60W).
Myotomy: an anterograde full-thickness dissection of the muscle layers was performed (Forced Coagulation 60W).
Closure of entry: the entry site was closed with clips.
Finally, the animals were administered painless euthanasia under the direct supervision of a veterinary.

**Data collection**
For each procedure, entry, tunnel and myotomy lengths and the number of clips for closure were collected. The procedural time and the duration of both the submucosal tunnel creation and myotomy were measured. Regarding adverse events (AE), the number of mucosotomies, presence of pneumomediastinum, presence of pneumoperitoneum, bleeding and intraprocedural death were registered.

**Definitions**
A technical success was considered when the myotomy was successfully completed. When hemostatic forceps (Coagrasper®; Olympus, Tokyo, Japan) were needed to control a hemorrhage, it was judged as a significant bleed. Intraprocedural death was defined as a death before the closure of the entry. Pneumomediastinum and pneumoperitoneum were taken into account if they were clinically significant with
hemodynamic instability, mechanical ventilation difficulty or the need of exsufflation. A mucosotomy was defined by the presence of an involuntary perforation of the mucosa.

Statistical analysis
Global outcomes such as technical success and AE rates were calculated. The median and interquartile range were calculated for quantitative variables. We compared the results from a first subgroup of cases (group A) with a second group (group B) in order to evaluate our progression throughout the training. Quantitative values were compared by the Mann-Whitney U test and qualitative values were compared by the Fisher exact test. Two tailed \( p \) values were considered as statistically significant if less than or equal to 0.05.

Clinical phase
POEM in humans suffering from achalasia or esophagogastric junction outflow obstruction (EGOO) (Chicago Classification) was implemented in our Unit under the supervision of an experienced endoscopist (JCMG/EAA) for the first five cases. Thereafter, fully independent POEM was performed. The technique was the same as in the preclinical phase, including a full-thickness myotomy approach, with the equivalent fungible, except for an ERBE VIO® 300D generator and an Olympus GIF-190H gastroscope. For type III achalasia, the length of the myotomy was defined by the hypercontractile segment seen on high-resolution manometry. All patients were intubated and in a supine position, and prophylactic antibiotics were administered. Clinical assessment ruled out complications and an esophagogram was performed only if clinical suspicion of an AE occurred.

High-resolution manometry was performed using a 36-channel, solid-state, catheter system with high-fidelity circumferential sensors at 1-cm intervals (Medtronic, Minneapolis, MN, USA). Data were analyzed using the ManoView™ software (Given Imaging, Yokne’am Illit, Israel) in the high-resolution esophageal color topography mode to standardize data analysis.
Data were collected regarding patient characteristics, pre-treatment diagnosis, Eckardt score pre and post-treatment and clinical gastroesophageal reflux (GERD) pre and post POEM. High-resolution manometry pre and post POEM, upper endoscopy post-POEM and 24h pH-metry post-POEM were prospectively recorded. Technical aspects during POEM, difficulties during the procedure and need for the intervention of the supervisor were also measured; AE were prospectively evaluated. All patients were prescribed proton pomp inhibitors twice daily during the first three months and treatment was withheld seven days before endoscopy, manometry and pH-metry.

Definitions
The procedural time was estimated from the insertion of the endoscope to clip closure. Clinical success was defined as an Eckardt score of ≤ 3 at the end of follow-up. Clinical GERD was measured by a GerdQ questionnaire pre and post POEM (no GERD < 8). An upper endoscopy performed at three and 12 months ruled out esophagitis (LA classification); 24h pH-metry defined abnormal acid exposure as a pH of < 4 for more than 4.5 % of the total time at three months and a year post POEM. A post-POEM manometry was performed three months after POEM, and integrated relaxation pressure (IRP4) normalization was defined if it was under the normal value (IRP4 < 15 mmHg).

RESULTS
Preclinical phase
Fifteen procedures were performed in live swine models (median weight was 40.5 kg, interquartile range 6) and the technical success was 100 % (Table 1). The results from a first group (n = 7) were compared with those of a second one (n = 8) and there were no differences in the time spent in each step (Fig. 1).

Regarding AE, there was a global decrease in the rate of EA from group A to group B during training. Pneumomediastinum (group A 71 % vs group B 37 %, p > 0.05) and pneumoperitoneum (group A 57 % vs group B 25 %, p > 0.05) were less frequent in group B, although the difference was not statistically significant. The mucosotomy rate
was similar in both groups. Finally, bleeding and death presented a noteworthy but non-statistically significant decrease (group A 57% vs group B 12%, p = 0.07 for both AE). After nine cases, a plateau in AE and death was observed.

Clinical phase
Eleven POEM procedures were performed (eight men, age 26-82) from June 2018 to December 2019, under supervision in the first five cases. The main indication was type II achalasia (63%) (Table 2). Technical success was 100%, with a median time of 124 minutes (interquartile range 65). In cases number 2 and 3, intervention of the proctoring endoscopist was required due to a difficult orientation at the EGJ. Without supervision, difficulties were encountered in cases 7 and 11 during tunneling at the level of the EGJ, reflected as an increase in procedural time, although technical and clinical success were achieved. There was one mild AE, a pneumoperitoneum (case number 3) that was resolved during the procedure by capnocentesis, with no clinical consequences.

During follow-up (3-21 months) (Table 3), there was a clinical success rate of 91% and the median Eckardt score decreased from 7.4 to 0.9. Normalization of the IRP4 was obtained in eight of ten patients (cases 7 and 8). None of our patients complained of GERD. In fact, the median GerdQ dropped from 9 to 1.2. Regarding objective reflux, 22% presented endoscopic esophagitis (all of them were Los Angeles grade B) and 25% had abnormal acid exposure measured by 24h pH-metry.

DISCUSSION
We report our process to create a POEM program in our Unit. The different steps of our training on animal models and the results in a second phase are described, with the application of the technique on humans, initially proctored by experienced endoscopist and then in a completely independent manner.

There is no consensus on what background the endoscopist should have before learning POEM. A training program might provide the necessary skills in POEM for western endoscopists, mitigating the limited experience in esophageal ESD (10-14). By contrast, it seems clearer where a POEM program should be implemented. Ideally, it
should be a referral center for esophageal motility disorders, with access to all the diagnostic tools such as high-resolution manometry, impedance and 24h pH-metry, etc. An appropriate multi-disciplinary team including radiologists, interventional radiologists, surgeons and thoracic surgeons is mandatory. Obviously, these teams should be made available 24 hours a day and Intensive Care Unit admission must be possible.

Training methods include live animals (*in vivo*) or extracted animal intestines (*ex vivo*) (15). There are several factors that limit their use such as accessibility, ethical issues, infection control, equipment for animal use only and costs. Some authors are developing non-biomaterial models, but its use is not globalized (16). We used live pigs because they are more accessible than *ex vivo* models. Although this implies a high cost, it has the advantage of being more realistic (e.g., the anatomical relation of the esophagus to adjacent organs, respiratory movements, presence of bleeding and air-related complications, etc.). However, there are differences in the esophagus between swine models and that of an achalasia patient. Even if we used relatively big pigs, the muscle layer of the esophagus is thinner, which makes it difficult to perform a selective dissection of the circular layer, which in turn facilitates the appearance of air-related AE. In addition, the submucosal space in pigs is softer and more easily dissected than in humans. Finally, pig models tend to bleed less than humans during submucosal dissection and myotomy due to a less vascularized esophagus.

There was no decrease regarding procedural time, in line with other publications (8,17). By contrast, others described a shorter time after 13 procedures (18). However, the procedural time is not the ideal measure of competence in POEM, but rather a marker of the endoscopist skills (18). The technical success and the rate of AE might be better indicators of efficiency. Air-related AE were higher than expected (19) but this may be due to the use of air insufflation instead of CO₂, which is mandatory in the clinical practice. Early studies using air insufflation reported rates of pneumomediastinum and pneumoperitoneum of 48 and 37 %, respectively (20,21). Unfortunately, CO₂ was not available for our training, which likely increased the rate of AE.
Bleeding was mild and easily manageable in all cases. This could be a bias of the model itself, as we know that it is poorly vascularized. The rate of mucosotomy was low from the beginning of training. Kurian et al. proposed using the mucosotomy rate as a marker of technical error and showed that it decreased as the endoscopist gained competency (9). However, Zein et al. found that the operator experience measured by case number did not correlate with the rate of accidental mucosotomy (18). Our data could be explained by the fact that the mucosal layer is thicker in pigs than in humans. Our first POEM procedures in the clinical practice were safely performed with no severe AE. Supervisor participation was required in two cases, as there were difficulties at EGJ, which is one of the most difficult steps. However, in the last six cases performed without supervision, although technical difficulties were found in cases number 7 and 11, technical success was achieved without AE. Orientation at the EGJ is one of the crucial steps during POEM and different hallmarks have been proposed for the identification of the EGJ, such as distance from incisors, palisade vessels, narrowing space, two penetrating vessels or oblique fibers. Some authors advocate for the use of a second endoscope in parallel to estimate tunnel and myotomy length in the gastric area. We did not evaluate this approach and we just used the standard hallmarks to identify the UEG. It could be of interest to study if this technique could make first POEM cases more effective, but this was beyond the aims of our study.

With our approach, we were able to perform the first POEM procedures, perhaps the most at risk for AE, in a safe manner. However, AE may appear in the future (22). Four patients without AE had a hospital stay longer than three days. These were our two first cases, in which we used a longer surveillance time to control eventual delayed AE. Additionally, case number 8 suffered a sinusitis not related to POEM with a difficult to control headache. Case number 9 was a patient who lived far from our hospital and an extra day of surveillance was advised.

Equally important, we obtained excellent clinical outcomes, with a clinical success rate of 91% and a significant improvement in the Eckardt score among all patients. However, there was no normalization of the IRP4 in two cases (no. 7 and 8), both performed without supervision. Case no. 8 was an EGGO, with a pre-POEM IRP4 of 26 mmHg falling to 16 mmHg (normal < 15 mmHg) and an Eckardt score which dropped
from 11 to 4. The most common cause of failure is incomplete myotomy of the lower esophageal sphincter. In this case of EGOO (an indication with lower success rates compared with achalasia), no subjective difficulties were encountered during POEM, procedural time was under the median time and myotomy length was 9 cm. By contrast, the hospital stay was longer than expected due to sinusitis not related to POEM, a previous treatment with toxin also failed and symptoms fluctuated during follow-up. Case no. 7 was a type II achalasia in which the clinical response was complete (Eckardt score 0). Perhaps a higher number of proctored cases could improve outcomes in manometry registries. However, our clinical outcomes were similar to those reported by referral centers.

Regarding GERD after POEM, we obtained a rate of esophagitis similar to that reported in literature, but a lower proportion of abnormal acid exposure and clinical GERD. This could be explained by the systematical use of proton pomp inhibitors during at least the first three months during follow-up.

Our study presents some limitations. First, a single endoscopist was trained and thus no generalization could be performed. By contrast, the endoscopist had limited experience in esophageal ESD, which may serve as a guide for other western endoscopists. Secondly, our model is far from perfect as we commented, although it allowed us to obtain initial competency in POEM. A technical limitation was the use of air insufflation in the preclinical phase. Finally, we performed POEM on a small number of patients, but the low rate of AE is remarkable with high rates of clinical success.

In summary, our study suggests that even in the setting of limited experience with esophageal ESD, training on a live swine model and proctoring of an experienced endoscopist during the first cases can provide the necessary skills to perform POEM.

ACKNOWLEDGMENTS
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REFERENCES
1. Inoue H, Minami H, Kobayashi Y, et al. Peroral endoscopic myotomy (POEM) for


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<table>
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<th>Case No.</th>
<th>Total time (min)</th>
<th>Tunnel time (min)</th>
<th>Myotomy time (min)</th>
<th>Entry length (cm)</th>
<th>Myotomy length (cm)</th>
<th>Adverse events</th>
<th>Type of adverse event</th>
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PP: pneumoperitoneum; PM: pneumomediastinum; B: bleeding; M: mucosotomy.
### Table 2: Clinical phase. Preoperative characteristics

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<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
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F: female; M: male; EGOO: esophagogastric outlet obstruction; GerdQ: Gastrointestinal Short Form Questionnaire.
### Table 3. Clinical phase. Intraprocedural and post-POEM characteristics

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<tr>
<th>Case No.</th>
<th>Time (min)</th>
<th>Myotomy length (cm)</th>
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<th>Hospital stay (days)</th>
<th>Eckardt post-POEM (points)</th>
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<th>IRP4 normalization</th>
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AE: adverse events; GerdQ: Gastrointestinal Short Form Questionnaire; IRP4: integrated relaxation pressure; B: B esophagitis of Los Angeles Classification.
Fig. 1. Preclinical phase. Procedural times. Boxes represent intraprocedural death (cases 1, 2, 3, 7 and 9).