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The efficacy of peroral endoscopic myotomy vs. pneumatic dilation as treatment for patients with achalasia suffering from persistent or recurrent symptoms after laparoscopic Heller myotomy. A RANDOMIZED CLINICAL TRIAL

Caroline M.G. Saleh, MD, Pietro Familiari, MD, Barbara A.J. Bastiaansen, MD, PhD, Paul Fockens, MD, PhD, Jan Tack, MD, PhD, Guy Boeckxstaens, MD, PhD, Raf Bisschops, MD, PhD, Aaltje Lei, BSc, Marlies P. Schijven, MD, PhD, Jan Guido Costamagna, MD, PhD, Albert J. Bredenoord, MD, PhD

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The efficacy of peroral endoscopic myotomy vs. pneumatic dilation as treatment for patients with achalasia suffering from persistent or recurrent symptoms after laparoscopic Heller myotomy.

A RANDOMIZED CLINICAL TRIAL

Short Title (max. 45 characters): POEM vs. PD after failed laparoscopic Heller myotomy.

Authors: Caroline M. G. Saleh, MD; Pietro Familiari, MD; Barbara A.J. Bastiaansen, MD, PhD; Paul Fockens, MD, PhD; Jan Tack, MD, PhD; Guy Boeckxstaens, MD, PhD; Raf Bisschops, MD, PhD; Aaltje Lei, BSc; Marlies P. Schijven, MD, PhD; Jan Guido Costamagna, MD, PhD; Albert J. Bredenoord MD, PhD;

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Abbreviations: Laparoscopic Heller myotomy (LHM), Pneumatic dilation (PD), Per-oral endoscopic myotomy (POEM).

Correspondence:

Albert J. Bredenoord, MD/PhD

Department of Gastroenterology & Hepatology

Academic University Medical Center

PO Box 22660, 1100 DD Amsterdam

The Netherlands

Telephone: +31 20 566 1745

Fax: +31 20 691 7033

E-mail: a.j.bredenoord@amsterdamumc.nl

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ABSTRACT (word count 260, max. 260)

Background & Aims For achalasia patients with persistent or recurrent symptoms after laparoscopic Heller myotomy (LHM), pneumatic dilation (PD) is the most frequently used treatment. Per-oral endoscopic myotomy (POEM) is increasingly being investigated as rescue therapy. This study aimed to determine the efficacy of POEM versus PD for patients with persistent or recurrent symptoms after LHM.

Methods This randomized multicenter controlled trial included patients after LHM with an Eckardt score >3 and significant stasis (≥2 cm) on timed barium esophagogram, randomized to POEM or PD. The primary outcome was treatment success, defined as an Eckardt score of ≤3, without unscheduled retreatment. Secondary outcomes included the presence of reflux esophagitis, HRM, and timed barium esophagogram findings. Follow-up duration was 1 year after initial treatment.

Results Ninety patients were included. POEM had a higher success rate (28 of 45 patients [62.2%]) than PD (12 of 45 patients [26.7%] (absolute difference, 35.6% [95%CI, 16.4%–54.7%]; [*p*=0.001); OR, 0.22 [95%CI, 0.09–0.54]; RR for success 2.33 [95%CI, 1.37–3.99]. Reflux esophagitis was not significantly different between POEM (12 of 35 [34.3%]) and PD (6 of 40 [15%]). Basal LES pressure and IRP-4 were significantly lower in the POEM group [*p*=0.034; *p*=0.002]. Barium column height after 2 and 5 minutes was significantly less in patients treated with POEM [*p*=0.005; *p*=0.015].

Conclusion Among achalasia patients with persistent or recurrent symptoms after LHM, POEM resulted in a significantly higher success rate than PD, with a numerically higher incidence of grade A-B reflux esophagitis.

Keywords: per-oral endoscopic myotomy; pneumatic dilation; laparoscopic Heller myotomy; Eckardt score; high-resolution manometry.

Clinical trial registry website & trial number: Trial NL4361 (NTR4501),

https://trialsearch.who.int/Trial2.aspx?TrialID=NTR4501

INTRODUCTION

Achalasia is a rare esophageal motility disorder characterized by dysfunctional or absent motility of the esophageal body and insufficient relaxation of the lower esophageal sphincter (LES). Treatment options for achalasia patients include the traditional pneumatic dilation (PD), laparoscopic Heller myotomy (LHM), and per-oral endoscopic myotomy (POEM). POEM and LHM provide longer-lasting symptomatic responses in treatment-naïve achalasia patients than a single series of PDs[1,2]. Despite the high efficacy rates of POEM and LHM, persistent or recurrent symptoms occur in 10-20% of patients treated with LHM[3,4].

Until now, treatment of persistent or recurrent symptoms after LHM remains controversial. Rescue therapy includes PD, revisional LHM, POEM, and as a last resort, esophagectomy[3,5–11]. Studies investigating the efficacy of PD for recurrent or persistent symptoms after LHM show a variable success rate ranging from 57-96%[12–15]. A retrospective study conducted in our center showed a long-term success rate of 57%. Revisional LHM has a reported efficacy of 71-90%[16–19]. However, this procedure requires extensive expertise as it is invasive with more difficulties due to adhesions, fibrosis, and the loss of tissue planes in the area of the gastric esophageal junction (GEJ) caused by the original operation[10,19]. The latter may support a preference to initially treat persistent or recurrent symptoms with PD before moving on to a revisional LHM, even though multiple PDs may be required[10].

Over the past decade, POEM gained acceptance as an endoscopic alternative to LHM for the primary treatment of achalasia. Considering the technique and its high efficacy rates, POEM is increasingly being investigated as a rescue therapy for patients suffering from persistent or recurrent symptoms after LHM. Case series suggest that POEM has an efficacy ranging from 81-100% when applied as rescue therapy after LHM[20,21]. Unfortunately, these studies represent small series with relatively short follow-up times and retrospectively collected data. More importantly, no studies have compared POEM to other performed rescue therapies, such as the most widely used PD.

Therefore, this study aimed to determine and compare the efficacy of POEM versus PD for patients suffering from persistent or recurrent symptoms after LHM.

METHODS

Study design

This study was designed as a multicenter randomized controlled trial. Inclusion occurred in 3 achalasia expert centers in the Netherlands, Belgium, and Italy, from January 2014 to June 2020. The institutional medical ethics board approved the study protocol in each hospital.

Patients were enrolled in the study after obtaining written informed consent. The primary endpoint was measured at 1-year follow-up. Follow-up of patients took place at 3 months and 1 year after initial treatment.

A data and safety monitoring board consisting of a methodologist, surgeon, and gastroenterologist was installed to monitor the safety and efficacy of treatment groups. Moreover, the study underwent an extensive randomly assigned internal quality audit in May 2017. Study sites were monitored by a research nurse, in which the CRFs and source data were checked.

This study was not classified as single-blind; to minimize bias several interventions were implemented. First of all, questionnaires were filled in by patients without the presence of research personnel. Diagnostic measurements were evaluated by an observer unaware of the patients' treatment. The interpretation whether an unscheduled treatment was indicated was solely based on a previously set cut-off.

All authors had access to the study data and reviewed and approved the final manuscript.

Patients and in- and exclusion criteria

Adult patients aged 18 to 80 years were eligible for enrollment if they had persistent or recurrent symptoms after LHM, defined as having an Eckardt symptom score greater than 3 in combination with significant stasis (≥2 cm) seen on timed barium esophagogram after 2 minutes.

Exclusion criteria included: previous PDs after LHM, previous (attempt at) POEM, previous surgery to the stomach or esophagus (except for LHM), known coagulopathy, presence of liver cirrhosis and/or esophageal varices, eosinophilic esophagitis, stricture of the esophagus, (pre)malignant esophageal lesions, one or more esophageal diverticuli and pregnancy at time of treatment.

Randomization

Randomization was done using a web-based program (ALEA Clinical B.V.) that assigned patients to POEM or PD in a 1:1 ratio, stratified according to the research site. Local study staff enrolled the patients. The number of patients treated with POEM or PD was similar for each center.

Interventions

Pneumatic dilation (PD)

For PDs, a series of dilations with Rigiflex balloons (Boston Scientific, MA, USA) was performed. Under fluoroscopic guidance, the balloon was positioned at the gastric esophageal junction and dilated at a pressure of 5 PSI for 1 minute, followed by 7 psi for 1 minute[22]. A graded distension protocol was implemented; initial PD was performed using a 30-mm balloon and, 1-3 weeks later, a subsequent 35-mm balloon dilation. In case of symptom persistence or recurrence within 3 months, a PD with a 40-mm balloon was performed. Patients presenting with symptom recurrence between 3 and 12 months after inclusion were offered additional PD treatment with a 35- and 40-mm balloon. If the treating physician judged that repeating a 30-mm PD was required before performing the 35-mm PD, this was allowed. PD was considered a failure in case of symptom persistence or recurrence after this additional round of PDs. All further retreatments with PD were considered unscheduled retreatments. Patients undergoing unscheduled PD retreatments were considered failures at one-year follow-up regardless of their Eckardt score at one-year follow-up. Thus, all patients randomized to the PD treatment arm received at least 2 dilations, with the last dilation of at least 35-mm dilation. PDs were performed by experienced endoscopists who completed >20 PDs independently.

Preprocedural instructions consisted of a liquid diet for 3 days prior to PD, which included a clear liquid diet 24 hours before and nil per mouth 8 hours before PD. Post PD, patients were prescribed a PPI once a day for 2 weeks after each dilation.

Per-oral Endoscopic Myotomy (POEM)

POEM was performed under general anesthesia, including endotracheal intubation, with the patient in a supine position. The POEM procedure was performed as described by Ponds et al.[22]; however, the mucosal incision, tunnel, and myotomy were slightly more towards the posterior orientation of the esophagus to stay away from the original myotomy scar. Patients randomized to undergo POEM

received the same preprocedural instructions as those who underwent PD. Admission took place on the same day as treatment or the day before, depending on the travel distance to the hospital, and discharged at least 1 day after POEM. Before treatment, patients were administered prophylactic antibiotics according to local hospital recommendations and a double-dose PPI intravenously. Post-discharge patients were advised to adhere to a liquid diet for 7 days followed by a soft diet for 1 more week and were prescribed a single dose PPI for 2 weeks.

Outcomes

The primary outcome, set as treatment success after 1-year follow-up, was defined as an Eckardt score of ≤3 without any unscheduled retreatment. For patients randomized to the PD treatment arm, this meant dilation with a 30- and 35-mm balloon and possibly PDs up to 40-mm; for patients randomized to the POEM arm, this meant undergoing POEM without any PDs or other unscheduled retreatments.

Secondary outcomes were assessed at baseline, after 3 months, and 1-year follow-up time. The quality of life and the achalasia-specific quality of life were measured using the Medical Outcomes Study 36-Item-Short Form Health Survey (SF-36) and the achalasia-specific quality of life questionnaire (Achalasia-DSQoL). The SF-36 measured general quality of life by scoring mental and physical aspects, ranging from 0 to 100, with higher scores indicating a better quality of life[23]. The presence of reflux symptoms and reflux esophagitis was assessed using the Gastroesophageal Reflux Disease Questionnaire (GERDQ) and upper endoscopy; the use of acid suppressant drugs was also documented. Esophageal stasis, as seen on the timed barium esophagogram, was measured.

All adverse events (AEs) and serious adverse events (SAEs) were documented. Treatment complications were defined as any adverse events that arose following the treatment or secondary to the treatment. Adverse events were classified as 'severe' when these resulted in (prolonged) admission of >24 hours, medium or intensive care unit admission, additional endoscopic procedures, blood transfusion, or death. Other complications were classified as 'mild'.

Clinical assessment and follow-up

The clinical assessment started at baseline and included a medical history, physical examination, and routine laboratory tests. Patients completed the GERDQ, SF-36, and achalasia-DSQoL questionnaires. High-resolution manometry (HRM) was performed to confirm the reoccurrence of achalasia[24]. Upper

endoscopy and timed barium esophagogram were performed to quantify esophageal stasis by measuring barium column height at 0, 1, 2, and 5 minutes on radiographic images after ingestion of 100-200ml of low-density barium sulfate suspension during a time window of 30-60 seconds[25].

Symptoms (Eckardt score) and questionnaires were assessed at 3-months and 1-year follow-up. HRM and timed barium esophagogram were obtained after 3-months and 1-years follow-up, whereas upper endoscopy was only performed after 1-year follow. The severity of reflux esophagitis was scored according to the Los Angeles classification[26]. PPI use was documented and was prescribed for patients who experienced reflux symptoms independent of follow-up time or when reflux esophagitis was observed during upper endoscopy.

Retreatment after unsuccessful treatments

Patients randomized to the PD treatment arm were initially treated with a 30- and 35-mm balloon. A 3-week follow-up point was set to assess symptom severity; in case of an Eckardt score >3, patients were treated with a 40-mm PD. If symptoms recurred within 1 year, patients were treated with additional PDs, up to a max. diameter of 40-mm. Patients were offered POEM if symptoms persisted or recurred after 1 year or if they refused additional or unscheduled retreatment with PDs within 1 year from initial PD treatment.

Patients who failed after POEM treatment were offered unscheduled retreatment consisting of PDs, according to the graded distension protocol described above.

Follow-up after retreatment was continued according to the initial treatment protocol.

Statistical methods

Sample size calculation was based on the reported long-term success rates of PD after Heller myotomy and the reported short-term success rates of POEM after Heller myotomy, 50-67% and respectively 91-100%[27–29]. One study in previously non-surgically treated patients showed a success rate of 82% after 12-month follow-up[30]. Therefore, we assumed long-term success rates of 58% for PD and 85% for POEM after Heller myotomy. With these success rates, we estimated that with 43 patients in each group, the study would have 80% power to detect a significant difference in success rate between PD and POEM, with a 2-sided alpha level of 0.05. To cope with an estimated 5% loss to follow-up, we aimed to enroll 90 patients.

Primary analysis

An intention-to-treat analysis was performed containing all patients as randomized to their treatment group. According to distribution, continuous data are presented as mean (SD) or median (interquartile range, IQR). Categorical data are presented as percentages.

The primary outcome included treatment effectivity, based on the Eckardt score at 1-year follow-up without retreatment. A Fisher's Exact Test was used to calculate the odds ratio and relative risk for treatment outcome and treatment-related SAEs.

The secondary outcomes were analyzed using a Mann-Whitney U test for continuous data or Fisher's exact test for categorical data.

Absolute differences of comparative results were calculated by subtracting percentages, means, or medians of the groups and calculating the 95% confidence intervals of the difference.

Post-hoc sensitivity analysis

To increase the credibility of the results, a sensitivity analysis was performed[31]. For the primary outcome, a per-protocol analysis was used. For the secondary outcomes, the post-hoc analysis included the use of linear mixed models and generalized linear models to account for missing values and to adjust for repeated effects or possible confounders. Specifically, linear mixed models were used to analyze the effect of treatment type on continuous secondary outcome parameters with fixed effects for time and treatment. An unstructured covariance structure was used when running the linear mixed models. The generalized linear models were used to analyze the association between treatment on binary outcome parameters, such as the presence of reflux esophagitis or PPI use. The generalized linear models used a binomial distribution and logit link function.

RESULTS

Enrollment and patient characteristics

Between January 2014 and June 2020, 90 achalasia patients with persistent or recurrent symptoms after LHM were randomized, of whom 45 were randomly assigned to receive POEM and 45 were assigned to receive PD (Figure 1). All patients were treated with LHM and a Dor fundoplication. One patient randomized to POEM never received treatment. In 2 patients, the myotomy as part of POEM was not possible because the submucosal tunnel could not be created due to submucosal fibrosis (Figure 1). A protocol deviation occurred related to the PD treatment as one patient received a single 30-mm PD and refused further treatment because of a significant reduction of symptoms. The final date of the 1-year follow-up period of the last patient was June 2021. Baseline characteristics were similar between groups (Table 1).

Primary Outcome

Analysis of the primary outcome showed higher treatment success at 1-year follow-up in the patients treated with POEM (28 of 45 patients [62.2%]) compared to the patients treated with PD (12 of 45 patients [26.7%] (absolute difference, 35.6% % [95% CI, 16.4% - 54.7%]; [p = 0.001); OR, 0.22 [95% CI, 0.09 – 0.54]; RR for success 2.33 [95% CI, 1.37 – 3.99]; (Figure 2 and Table 2). A total of 5 missing values were observed, which were assumed failures according to the intention-to-treat principle (Figure 2; Supplement 1 Figure 1). Single imputations were used for 3 missing values by logically inferencing: 2 patients were considered successful at 1-year as they were successfully treated at 3-months and 2-year follow-up (without any retreatments), and 1 patient was deemed a failure as this patient was a failure at 3-months.

In the patients randomized to POEM, 3 patients did not undergo a complete POEM: 2 patients did not receive POEM because fibrotic submucosa prohibited the creation of a submucosal tunnel and performance of the endoscopic myotomy, and 1 patient was lost to follow-up after randomization (Figure 1).

In the patients randomized to PD, 1 patient only underwent a single 30-mm PD with a good response and refused further dilation with a 35-mm balloon. The other patients received dilations with 30- and 35-mm balloons (n=19) or up to 40-mm (n=25). Waist obliteration was obtained in all PDs.

Secondary Outcomes

Reflux Esophagitis, PPI Use, and Reflux Symptoms (GERDQ)

At 1-year follow-up, a numerically higher incidence of reflux esophagitis was observed in patients treated with POEM (12 of 35 [34.3%]) than PD (6 of 40 [15%]); but this was not statistically significant. Further specified, for the patients randomized to POEM, 11 of 12 [91.7%] were assigned grade A-B, and 1 [8.3%] grade C, whereas for patients randomized to PD, 5 of 6 [83.3%] were assigned grade A-B and 1 [16.7%] grade C. Reflux symptoms and daily use of PPI did not differ between treatment groups (Table 3 and Figure 4; Supplement 1 Table 1).

Eckardt Score, HRM, timed Barium Esophagogram, and Quality of Life (ADSQoL& SF-36)

This study found a significantly lower Eckardt score was measured in the patients treated with POEM versus those treated with PD [p = 0.016] (Figure 3 and Supplement Table 1). Basal LES pressure and IRP-4 were significantly lower at 1-year follow-up for patients treated with POEM versus patients treated with PD [p = 0.034; p = 0.002]. A significant difference was found between POEM and PD for barium column height after 2 and 5 minutes, with less stasis observed in the POEM group [p = 0.005; p = 0.015]. There was no significant difference between POEM and PD when evaluating the maximum esophageal width measured during timed barium esophagogram [p = 0.121] (Figure 4 and Supplement Table 1).

With regards to the baseline measurements, this study found no significant differences in median Eckardt score [*p = 0.920*], basal LES pressures [*p = 0.109*], IRP-4 [*p = 0.631*], achalasia subtypes [*p = 0.927*], barium column height after 2 [*p = 0.282*] and 5 minutes [*p = 0.830*], between un- and successfully treated patients. The same applied when performing subgroup analysis within the treatment groups; for patients treated with POEM and respectively PD, there were no significant differences in median Eckardt score [*p = 0.910*; *p = 0.699*], basal LES pressures [*p = 1.0*; *p = 0.501*], IRP-4 [*p = 0.756*; *p = 0.926*], achalasia subtypes [*p = 0.765*; *p = 0.843*], barium column height after 2 [*p = 0.597*; *p = 0.669*] and 5 minutes [*p = 0.597*; *p = 0.830*], between un- and successfully treated patients.

Importantly, our study showed a significantly lower mean Achalasia-DSQoL score in the POEM group. The overall quality of life was measured using the SF-36 score, composed of 8 sections. There was a significant difference between POEM and PD, favoring POEM for Physical Functioning, Emotional well-being, and Social Functioning. For the components General Health, Limitations due to Physical Health,

Limitations due to Emotional problems, Energy/Fatigue, and Pain, this study found no difference (Table 3).

Serious Adverse Events (SAEs) and Adverse Events (AEs)

Eight SAEs occurred during the study, 2 were related to treatment, and 6 occurred independently of the study intervention. One micro-perforation occurred after a POEM, which required admission and treatment with antibiotics for 2 days with subsequent discharge; this patient was initially randomized and treated with PD and failed. Another SAE consisted of chronic severe reflux symptoms after PD and was treated with a Toupet fundoplication. Both patients continued in the study. Detailed information on SAEs independent of the study interventions is provided in Supplement 2.

Adverse events were more common after POEM (14 of 45 patients [31.1%]) vs. PD (9 of 45 [20%]). AEs in the POEM group were related to Candida esophagitis (n = 1), Helicobacter pylori infection (n = 3), peri-procedural mucosal bleeding (n = 2), gastric perforations (1 caused by the spray catheter that was managed conservatively and 1 that was treated by placement of 3 clips) (n = 2), food impaction (n = 1), and several not upper-GI related AEs (n = 5).

In the PD group, reported AEs were retrosternal pain after PD (n = 2), pneumoperitoneum and subcutaneous emphysema after PD (n = 1), mild bleeding during PD managed conservatively (n = 1), an allergic reaction after endoscopy (n = 1) and not upper-GI related AEs (n = 4).

Post hoc sensitivity analysis

Primary outcome

Post hoc sensitivity analysis of the primary outcome was performed by looking at the data with the 'per-protocol' principle. Within the POEM group, 2 patients received PD as the primary treatment after randomization to POEM because of fibrotic mucosa, which prohibited the performance of POEM. Furthermore, 1 patient was lost to follow-up after treatment with POEM, and 1 was lost to follow-up after randomization. Within the POEM group, 27 out of 41 patients [65.8%]) versus 12 of 47 [25.5%] in the PD group were successfully treated at 1-year follow-up (absolute difference, 40.3% [95% CI, 21.2% - 59.5%]; relative risk, 2.6 [95% CI, 1.51 – 4.41]).

In the PD group, 14 patients received retreatment with POEM; 6 of 14 [42.9%] were successfully treated at 1-year follow-up. Within the POEM group, 2 patients received retreatment with PD, and both failed.

Secondary outcomes

Linear mixed models were used to determine the difference in treatment effect on secondary outcomes. The differences are represented as parameter estimates (Supplement Table 1 and Table 3). Linear mixed models adjusted for time showed a significant difference in Eckardt score, basal LES pressure, IRP-4, and barium contrast height at T = 2 and 5 minutes, at 1-year follow-up in favor of POEM. This study did not find significant differences in the maximum esophageal width measured during timed barium esophagogram between POEM and PD using linear mixed models. With regards to the Achalasia-DSQoL and SF-36 scores, linear mixed models showed similar results as the classical statistical analysis (Table 3).

By using generalized linear models, the association between treatment and binary outcomes such as the occurrence of reflux esophagitis and reflux symptoms could be determined. The strength of this association is represented as a β-coefficient. With the generalized linear model, it was also possible to adjust for certain confounding factors, such as PPI use within the first year of follow-up. Both with and without adjustment, there was no significant association between treatment and the occurrence of reflux esophagitis and reflux symptoms (Supplement Table 1). The same applies to the use of a PPI within the first year of follow-up (Supplement Table 1). These results fall in line with the classical statistical analysis presented above and thereby show consistent results.

DISCUSSION

This randomized controlled clinical study demonstrated that for achalasia patients with persistent or recurrent symptoms after LHM, POEM is more efficacious than PD as rescue therapy.

Regarding the secondary outcome parameters, this study found significant differences in LES-pressure, IRP-4, and barium height at T = 2 and 5 minutes, in favor of POEM at 1-year follow-up. Importantly, no statistically significant differences between groups were measured for occurrence of reflux esophagitis, PPI use and reflux symptoms. When looking at treatment effect on the quality of life, a significant difference in achalasia-DSQOL score was found, again favoring POEM. However, for quality of life measured by the SF-36, significant differences were observed for only 3 out of 8 components: Physical functioning, Emotional well-being, and Social functioning.

With respect to safety, there were 2 treatment-related SAEs: a microperforation caused by POEM, which was treated with antibiotics and 2 days of admission, and extreme reflux symptoms as a result of PD which were treated with a Toupet fundoplication. In contrast to studies comparing POEM and PD for treatment-naïve achalasia patients, this study did not find a statistically significant difference in the development of reflux esophagitis, the experience of reflux symptoms, and the use of PPI between patients treated with POEM or PD[22].

This is the first randomized controlled trial that compared POEM with PD as the treatment of achalasia patients with persistent or recurrent symptoms after LHM. The efficacy of POEM observed in our study, 62.2%, is less compared to the uncontrolled prospective and retrospective studies, where clinical success rates range between 81 – 96%[9,20,28,32–36]. This discrepancy cannot be attributed to a difference in the definition of success, as these studies also defined clinical success as an Eckardt score less than or equal to 3. However, most of these studies included small samples, had a retrospective design in which inclusion to the cohort was determined afterward and presented shorter follow-up times, which could explain higher success rates[8,9,37]. This study's observed success rate of 62.2% at 1-year should be considered a medium-term outcome. Longer follow-up data will help provide information about the duration of the treatment effect. Moreover, our data confirm the low-risk nature of POEM.

As for PD, this study observed an efficacy rate of 26.7%, which is also lower than the efficacy reported by published case series, where efficacy ranges from 57-96%[9,12,15,17,38]. One reason for this discrepancy could be the heterogeneity of PD protocols used and the retrospective nature of most published reports.

In this study, patients were initially treated with 30- and 35-mm PD (except for 1 patient), and in case of persistent symptoms after 3 weeks, an additional 40-mm PD was performed. If symptoms recurred within 1 year, patients were treated with another round of PDs. Repeat series of PD is an accepted clinical strategy and reflects daily practice. Still, patients may experience another series of PDs as failed treatment. Indeed, in this study, a few patients randomized to the PD arm refused additional rounds of PD when they experienced persistent or recurrent symptoms after their first round of PD. These patients were considered failures, and some received POEM in consultation with their physician; 14 patients were retreated with POEM after failed PDs within their first-year follow-up. Furthermore, in this study, pressurization of balloons started at 5 PSI for 1 minute, followed by 7 PSI for another minute. Though this might differ from other protocols, it is important to realize waist obliteration was obtained in all PDs, most of these already occurring with 5 PSI. Therefore, it was considered unlikely that the difference in pressurizations used played a role in the high degree of PD failure.

Although POEM is more invasive and requires more technical endoscopic skills, the risk of severe complications was not higher than seen with PD. Data from this study suggest that in previously treated achalasia patients, POEM did lead to more grade A-B reflux esophagitis, even though this was not statistically significant. This was most likely the result of the small number of events in this subgroup analysis. On the other hand, POEM did not conduce more reflux symptoms or PPI use than PD. Interestingly, it was after a series of PD that one patient experienced severe reflux symptoms that required a Toupet fundoplication.

Taking into account the efficacy rate, the occurrence of complications, and the presence of reflux esophagitis and reflux symptoms within the clinical context, it seems reasonable to offer POEM as primary treatment option for achalasia patients suffering from persistent or recurrent symptoms after LHM based.

Strengths & Limitations

The strengths of this randomized controlled trial are the substantial number of patients included, particularly given the rare nature of this disorder, and the stratification of the randomization by center. In addition, this study used objective measures at baseline to determine the nature of the persistent or recurrent symptoms and the eligibility for the trial. The objective measures were also used to analyze treatment effect and esophageal function. Concerning the statistical methods: primary data analysis

was performed according to the intention-to-treat principle. Nonetheless, to increase the credibility and strength of the forthcoming conclusions, a sensitivity analysis was implemented[31].

There were also limitations identified. Firstly, primary and secondary outcomes were assessed at 1-year follow-up. Consequently, no conclusions can be drawn for longer-term treatment success, which is important given that achalasia is a lifelong chronic disease. Second, like most endoscopic or surgical studies that evaluate new interventional techniques, patients and caregivers were not blinded for treatment allocation. Even though a blinded study would have been very challenging – requiring general anesthesia and admission for the PD group and undergoing several sham PDs in the POEM group – bias was minimized to the greatest extent possible by blinding observers of diagnostic measurements for the patients' treatment; questionnaires were filled in by patients without the presence of research personnel; indication for an unscheduled treatment was solely based on the previously set cut-off, namely Eckardt score >3. Lastly, multiple PD sessions might form a potential bias in the comparison to 1 treatment intervention; however, as stated before, this was done deliberately to optimally reflect routine clinical care in these patients.

CONCLUSION

Among achalasia patients with persistent or recurrent symptoms after LHM, treatment with POEM resulted in a significantly higher success rate compared to PD, with a numerically (statistically not significant) higher incidence of grade A-B reflux esophagitis. These findings support the consideration of POEM as the initial treatment option for achalasia patients with persistent or recurrent symptoms after laparoscopic Heller myotomy.

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LEGENDS OF EMBEDDED FIGURES AND TABLES (EXCL. LEGENDS OF SUPPLEMENTAL MATERIAL)

Figure 1. Flowchart, randomization, and follow-up according to intention-to-treat analysis.

*1 This patient only underwent a PD with a 30-mm balloon because adequate symptom control (Eckardt score <3) was achieved after a single PD, the patient refused PD with a 35-mm balloon.

Figure 2. Primary outcome for POEM and PD (absolute numbers).

Figure 3. Mean Eckardt score over 1-year time for POEM and PD.

Figure 4. Mean Basal LES pressure, IRP-4, Barium Column height at 2- and 5-minutes over 1-year time, and presence of reflux esophagitis at 1-year follow-up for POEM and PD.

Table 1. Baseline characteristics of included patients presented per treatment group.

Abbreviations: Achalasia-DSQoL, achalasia-specific quality-of-life; GERDQ, gastroesophageal reflux disease questionnaire; IQR, interquartile range; SF-36, 36-Item Short-Form Health Survey.

*1 Eckardt score ranges from 0-12, with a higher score indicating more severe symptoms.

*2 Achalasia-DSQoL score ranges from 10-33, with a lower score indicating a better quality of life.

*3 SF-36 score consisted of a Physical Component Summary score and Mental Component Summary score, each ranging from 0-100, with higher scores indicating better quality of life.

Table 2. Primary outcome of patients with Achalasia at 1-year follow-up after POEM or PD as intention-to-treat analysis.

*1 POEM is less likely to result in failure than PD.

*2 Relative risk for success, success was 2.33 times more likely in patients randomized to receive POEM.

Table 3. Secondary objective outcomes after 1-year follow-up after POEM or PD.

*1 P-Value for the difference in outcome of continuous data analyzed using Mann Whitney U test and categorical data using χ^2 test between treatment groups at follow-up year 1.

*2 Parameter estimates represent the difference in outcome of continuous data between treatment groups at follow-up year 1, adjusted for repeated measurements over 1 year time; measured by linear mixed models with PD as the reference treatment.

*3 *P* Value for parameter estimates as measured by linear mixed models with PD as the reference treatment.

*4 β-coefficients represent the association between categorical data at follow-up year 1 and the treatment groups; measured by generalized linear models using PD as the reference treatment.

*5 *P* Value for β-coefficients as measured by generalized linear models with PD as the reference treatment.

*6 Results of generalized linear models adjusted for PPI use during 1st-year follow-up.

Characteristics (*n = 90*)	POEM (*n = 45*)	PD (*n = 45*)
Sex		
Female (% male)	27 (40%)	29 (35.6%)
Age (y), median (IQR)	53 (IQR: 29 – 77)	52 (IQR: 25 – 79)
Eckardt score*[1], median (IQR)	6 (IQR: 4 – 8)	6 (IQR: 4 – 6)
Achalasia subtypes		
Subtype I (*n =19*)	9 (47%)	10 (53%)
Subtype II (*n = 30*)	15 (50%)	15 (50%)
Subtype III (*n = 7*)	4 (57%)	3 (43%)
Basal LES pressure (mmHg), mean (CI)	22.7 (CI: 17.9 – 27.5)	25.4 (CI: 19.3 – 31.5)
Basal IRP-4 (mmHg), mean (CI)	17.2 (CI: 13.6 – 20.8)	21.3 (CI: 16.1 – 26.6)
Barium esophagogram		
Column height T = 2 min (cm), median (IQR)	4.7 (IQR: 1.9 – 7.5)	4.3 (IQR: 1 – 7.6)
Column height T = 5 min (cm), median (IQR)	3.4 (IQR: 0.3 – 6.5)	4.0 (IQR: 1.2 – 6.8)
Max. diameter (cm), median (IQR)	3.5 (IQR: 2.6 – 4.4)	3.3 (IQR: 2.1 – 4.7)
Achalasia-DSQoL score*[2], median (IQR)	25 (IQR: 25 – 27)	26 (IQR: 23 – 28)
SF-36 score*[3], median (IQR)		
General Health	50 (IQR: 35 – 70)	45 (IQR: 35 – 60)
Physical functioning	80 (IQR: 65 – 93.8)	82.5 (IQR: 57.5 – 95)
Limitations due to Physical health	25 (IQR: 0 – 100)	50 (IQR: 0 – 100)
Limitations due to Emotional problems	100 (IQR: 41.7 – 100)	66.7 (IQR: 0 – 100)
Energy/Fatigue	50 (IQR: 35 – 65)	42.5 (IQR: 30 – 60)
Emotional well-being	72 (IQR: 53 – 88)	70 (IQR: 37 – 84)
Social Functioning	75 (IQR: 50 – 87.5)	56.3 (IQR: 28.2 – 75)
Pain	57.5 (IQR: 45 – 80)	45 (IQR: 32.5 – 67.5)

Achalasia subtype total registered		
	Valid	Missing
POEM	28	17
PD	28	17
Total	56	34

Achalasia subtype			
		Failure	Success
POEM	Type I (*n=9*)	4 (44.4%)	5 (55.6%)
	Type II (*n=15*)	5 (33.3%)	10 (66.7%)
	Type III (*n=4*)	2 (50%)	2 (50%)
		Failure	Success
PD	Type I (*n=10*)	6 (60%)	4 (40%)
	Type II (*n=15*)	13 (86.7%)	2 (13.3%)
	Type III (*n=3*)	2 (66.7%)	1 (33.3%)
		Failure	Success
Total	Type I (*n=19*)	10 (52.6%)	9 (47.4%)
	Type II (*n=30*)	18 (60%)	12 (40%)
	Type III (*n=7*)	4 (57.1%)	3 (42.9%)

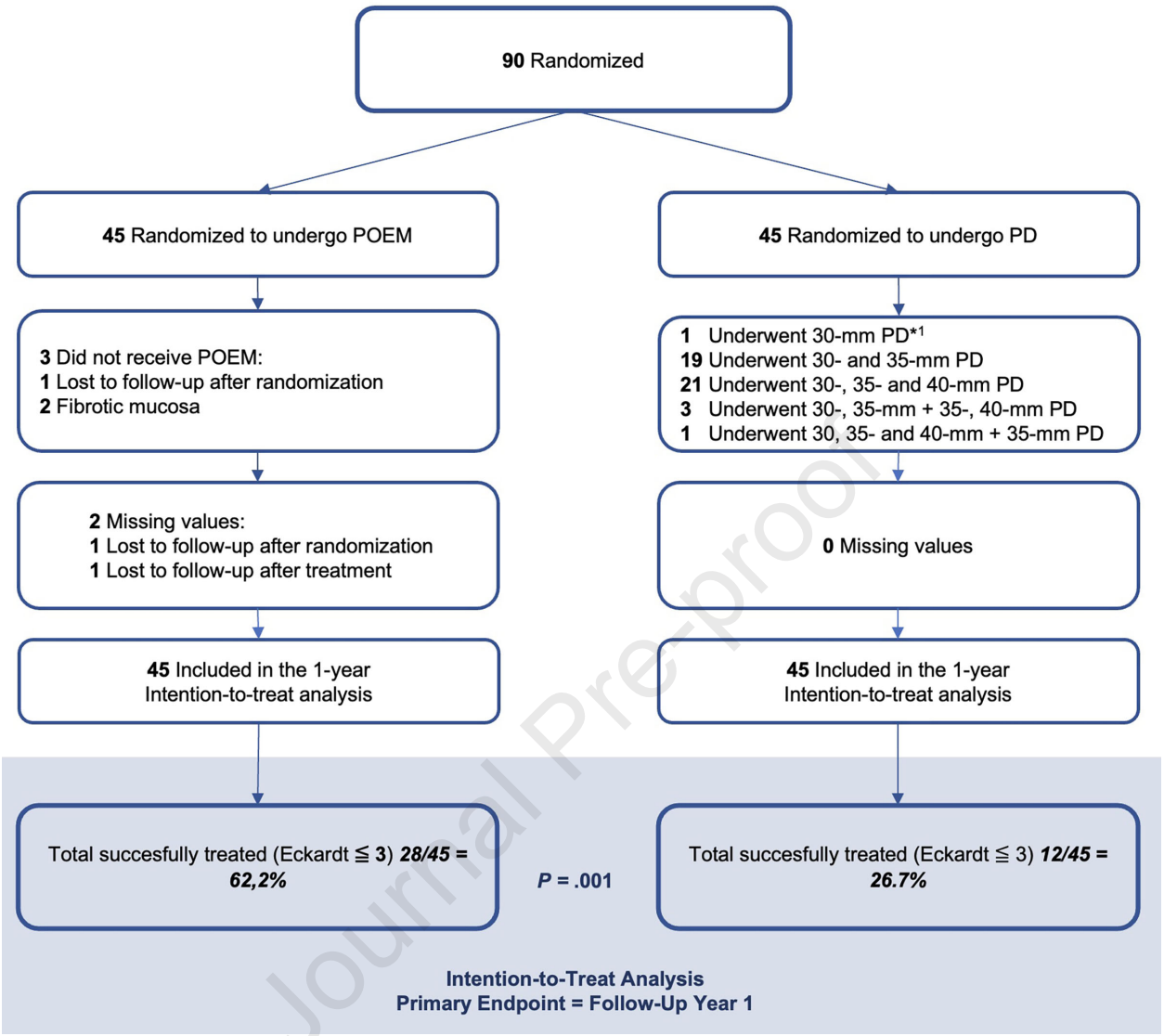
Achalasia subtype				
	POEM (*n=28*)	PD (*n=28*)	Total (*n=56*)	
Type I	9 (20%)	10 (22.2%)	19 (33.9%)	
Type II	15 (33.3%)	15 (33.3%)	30 (53.6%)	
Type III	4 (8.9%)	3 (6.7%)	7 (12.5%)	

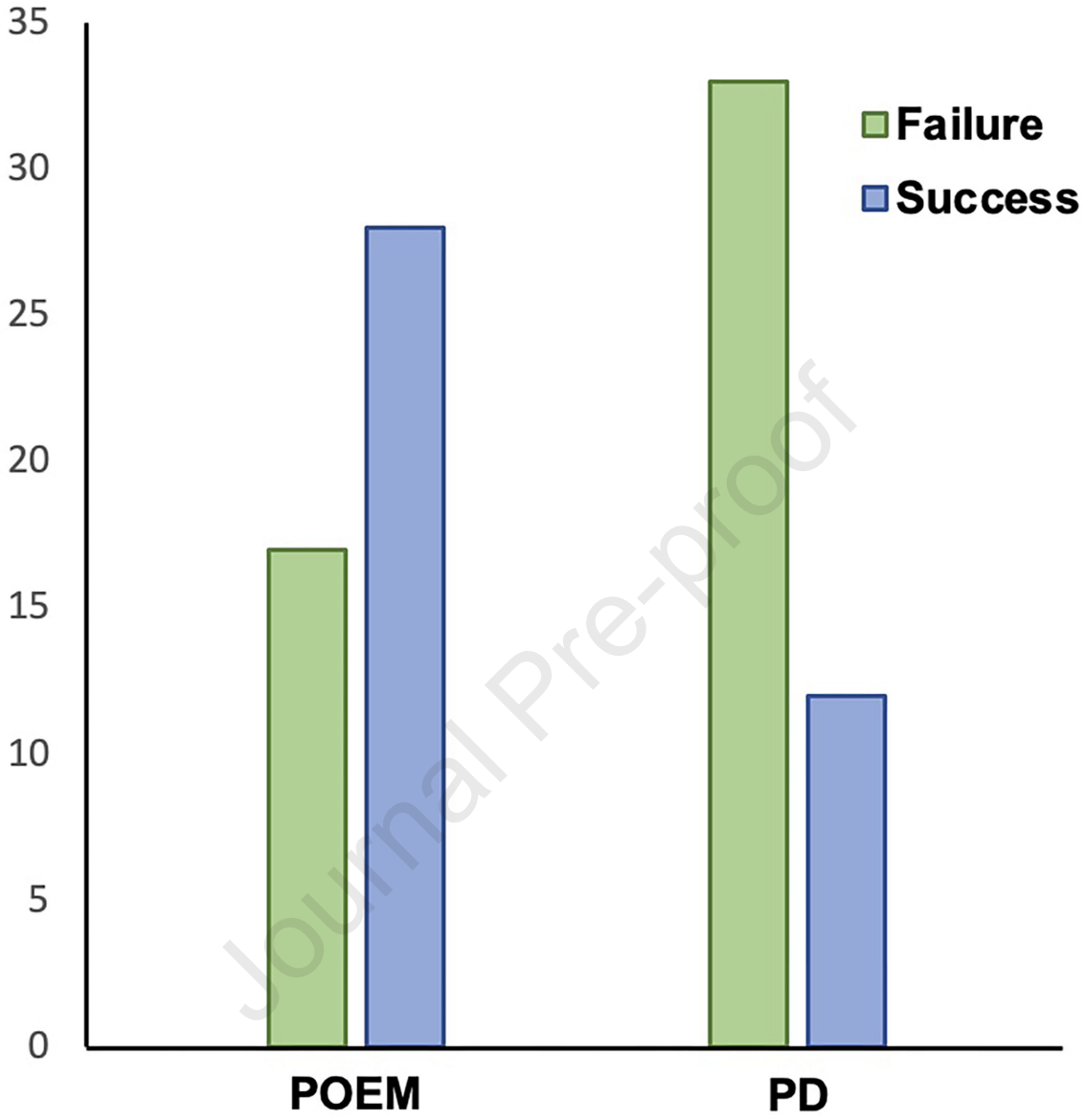
Achalasia subtype					
		Value	df	Asymptotic Significance (2-sided)	Exact Signifance (2-sided)
POEM	Pearson Chi-Square	0.516*[1]	2	0.773	0.765
	Fisher-Freeman-Halton Exact Test	0.725			0.765
		Value	df	Asymptotic Significance (2-sided)	Exact Signifance (2-sided)
PD	Pearson Chi-Square	0.491*[2]	2	0.782	0.843
	Fisher-Freeman-Halton Exact Test	0.759			0.843
		Value	df	Asymptotic Significance (2-sided)	Exact Signifance (2-sided)
Overall	Pearson Chi-Square	0.258*[3]	2	0.879	0.927
	Fisher-Freeman-Halton Exact Test	0.363			0.927

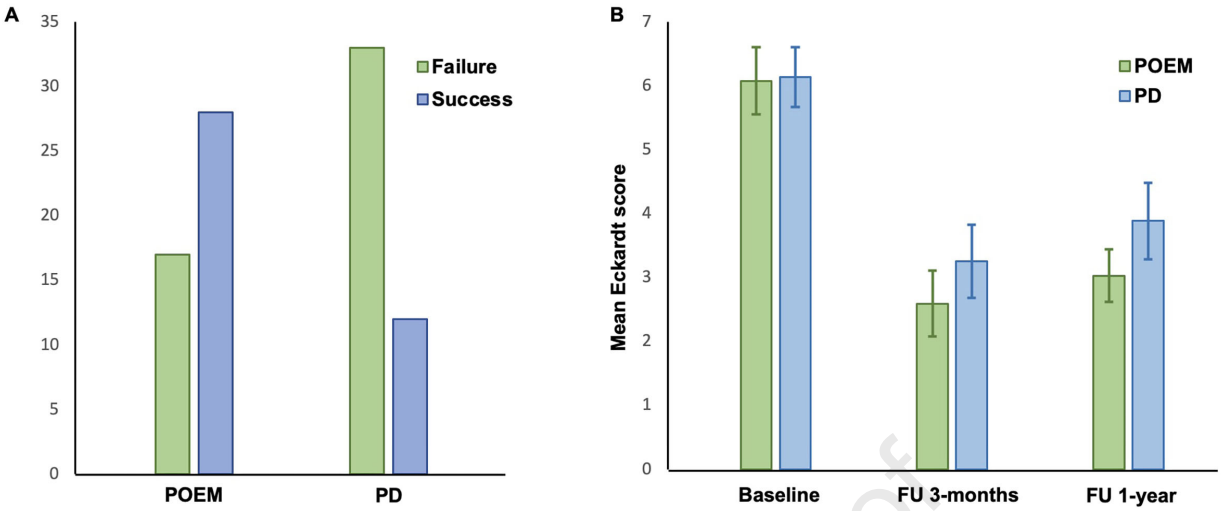
*[1] 3 cells (50,0%) have expected count less than 5. The minimum expected count is 1.57.
*[2] 4 cells (66,7%) have expected count less than 5. The minimum expected count is 0.96.
*[3] 2 cells (33,3%) have expected count less than 5. The minimum expected count is 3,00.

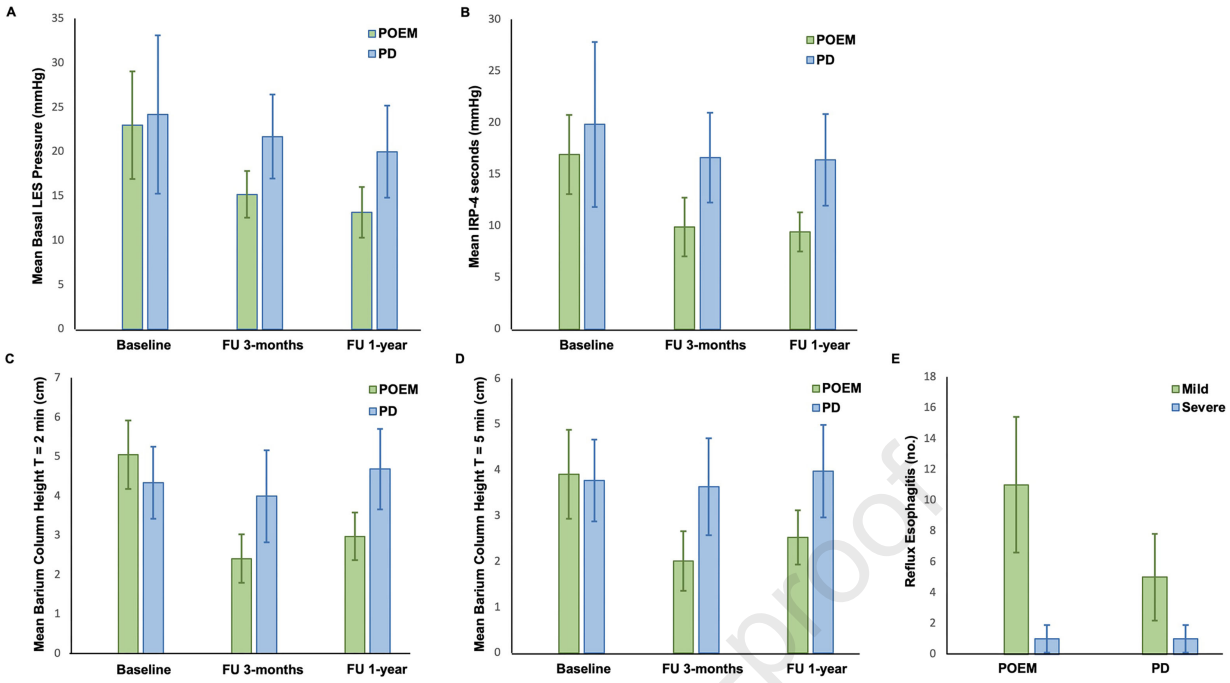
	POEM No. (%) (*n=45*)	**PD** No. (%) (*n=45*)	***P* Value**	**Odds ratio (OR), (95% CI)**	**Relative Risk (RR), (95% CI)**	**Unadjusted absolute difference** %, **(95% CI)**
1-year follow-up (primary endpoint)						
Overall treatment success	28 (62.2%)	12 (26.7%)	0.001	0.22 (0.09 – 0.54)*[1]	2.33 (1.37 – 3.99)*[2]	35.6%, (16.4% – 54.7%)

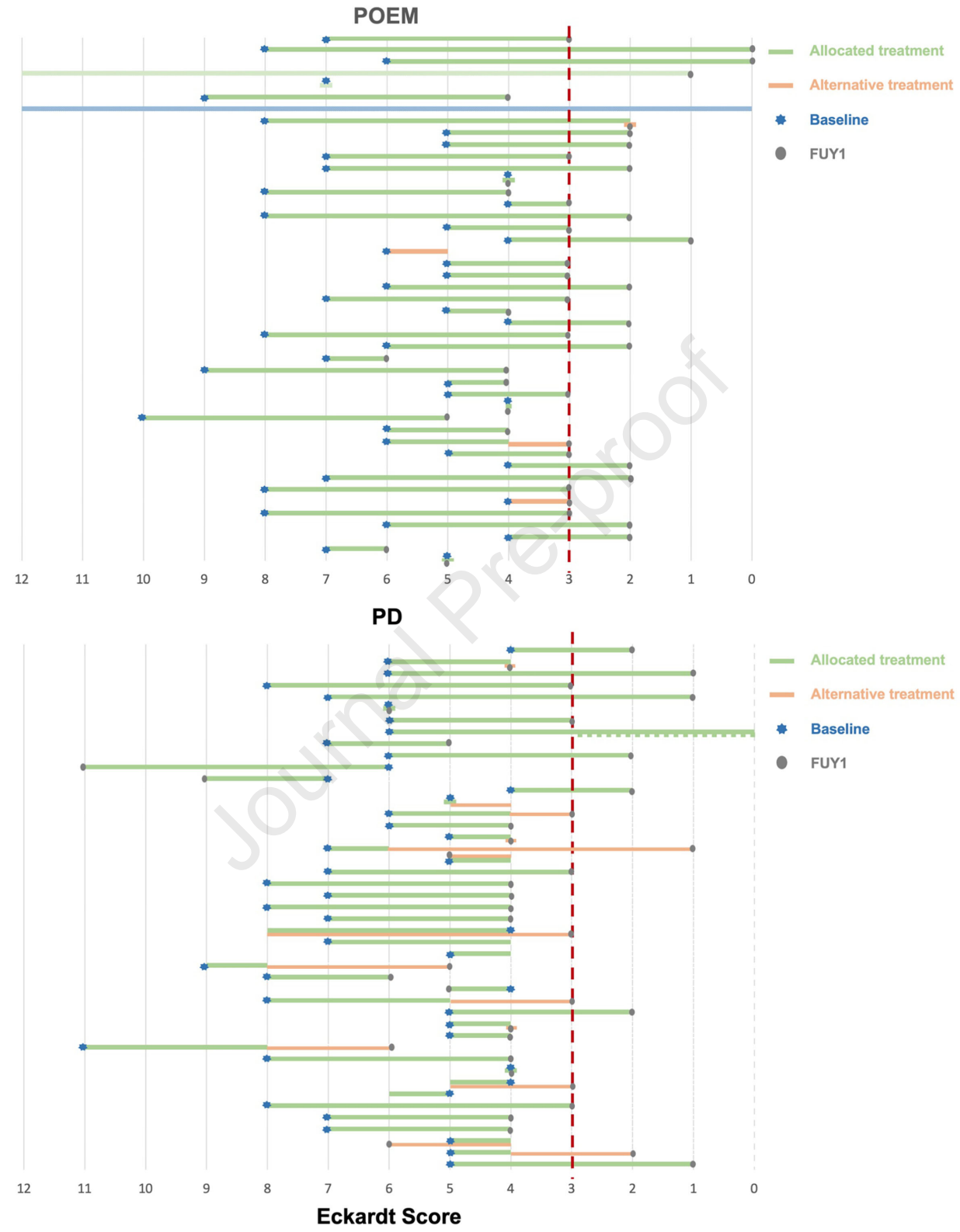
		POEM		PD			POEM vs. PD			
		Mean	SD	Mean	SD	*P* Value*[1]	Parameter estimate*[2]	SE	*P* Value*[3]	95% CI
Eckardt score		2.95	1.44	3.77	1.78	0.016	-0.788	0.361	0.031	-1.505 – -0.071
LES pressure		14.81	7.37	19.97	9.99	0.034	-4.95	2.41	0.043	-9.73 – -0.160
IRP-4 seconds		9.64	4.96	15.62	9.08	0.002	-5.998	1.727	0.001	-9.425 – -2.571
Barium Height T=2 min		2.97	1.74	4.64	2.90	0.005	-1.658	0.592	0.006	-2.833 – -0.483
Barium Height T=5 min		2.47	1.77	4.02	2.89	0.015	-1.558	0.592	0.01	-2.732 – -0.384
Max. Width		3.23	1.25	3.65	1.36	0.121	-0.363	0.283	0.203	-0.925 – 0.199
		No. (%)		No. (%)		*P* Value*[1]	β-coefficient*[4]	SE	*P* Value*[5]	95% CI
Reflux esophagitis (*n = 75*)		12/35 (34.3%)		6/40 (15%)		0.062	-0.770 (1.022*[6])	0.658 (1.398*[6])	0.242 (0.465*[6])	-2.06 – 0.530 (-3.762 – 1.718*[5])
	Grade A	7/35 (20%)		4/40 (10%)						
	Grade B	4/35 (11.4%)		1/40 (2.5%)						
	Grade C	1/35 (2.9%)		1/40 (2.5%)						
	Grade D	0 (0%)		0 (0%)						
PPI Use (*n = 87*)		29 (69%)		26 (57.8%)		0.374	-0.489	0.45	0.277	-1.37 – 0.393











Baseline Eckardt score unknown.

Lost to follow-up after randomisation to POEM, baseline Eckardt score unknown.

		POEM		PD			POEM vs. PD			
		Median	IQR	Median	IQR	*P* Value*[1]	Parameter estimate*[2]	SE	*P* Value*[3]	95% CI
Achalasia-DSQoL score		18	15 – 21.25	21	16.5 - 24	0.023	-2.535	1.046	0.017	-4.164 – -0.455
SF-36										
	General Health	65	36.25 - 80	52.5	45 – 75	0.636	3.258	4.902	0.508	-6.504 – 13.021
	Physical functioning	95	81.25 – 100	80	55 – 95	0.002	10.945	5.320	0.043	0.359 – 21.531
	Limitations due to Physical health	100	0 - 100	50	0 - 100	0.217	12.493	8.964	0.167	-5.333 – 30.319
	Limitations due to Emotional problems	100	33.3 - 100	100	0 - 100	0.110	12.838	8.703	0.144	-4.465 – 30.141
	Energy/Fatigue	62.5	45 – 82.5	55	42.5 – 72.5	0.334	5.597	4.938	0.260	-4.216 – 15.409
	Emotional well-being	84	76 – 92	76	48 – 84	0.007	12.458	4.294	0.005	-3.926 – 20.991
	Social Functioning	87.5	75 – 100	75	56.25 – 87.5	0.005	16.186	5.729	0.006	4.803 – 27.569
	Pain	77.5	60 – 90	67.5	45 – 90	0.096	9.459	5.263	0.076	-1.001 – 19.918
GERDQ		7	6 – 9.75	8	7 - 10	0.395	-0.500	0.587	0.396	-1.665 – 0.644
		No. (%)		No. (%)		*P* Value	β-coefficient*[4]	SE	*P* Value*[5]	95% CI
GERDQ ≥ **8**, No. (%) (*n* = *79*)		18/40 (45%)		22/39 (56.4%)		0.371	-0.458 (-0.649*[6])	0.453 (1.012*[6])	0.312 (0.521*[6])	-1.347 – 0.430 (-2.633 – 1.334*[6])

Supplement 1. Tables and figures

Table 1. Secondary subjective outcomes after 1-year follow-up time after POEM or PD.

Abbreviations: Achalasia-DSQoL, achalasia-specific quality-of-life; GERDQ, gastroesophageal reflux disease questionnaire; IQR, interquartile range; SF-36, 36-Item Short-Form Health Survey.

*1 *P* Value for the difference in outcome of continuous data analyzed using Mann Whitney U test and categorical data using χ^2 test between treatment groups at follow-up year 1.

*2 Parameter estimates represent the difference in outcome of continuous data between treatment groups at follow-up year 1, adjusted for repeated measurements over 1 year time; measured by linear mixed models with PD as the reference treatment.

*3 *P* Value for parameter estimates as measured by linear mixed models with PD as the reference treatment.

*4 β-coefficients represent the association between categorical data at follow-up year 1 and the treatment groups; measured by generalized linear models using PD as the reference treatment.

*5 *P* Value for β-coefficients as measured by generalized linear models with PD as the reference treatment.

*6 Results of generalized linear model adjusted for PPI use during 1st year follow-up.

Figure 1. Eckardt score range from baseline to follow-up year 1 for POEM and PD.

Supplement 2. Serious adverse events independent of study intervention

Within the group of patients treated with POEM there were 3 SAEs not related to intervention. One patient was hospitalized because of worsened dysphagia symptoms, which required placement of a feeding tube; symptoms resolved spontaneously, and the feeding tube could be removed swiftly. Another patient discovered an atrium septum defect type II (birth defect) during the trial, which was operatively treated. Lastly, one patient died due to liver cirrhosis and ischemic cardiomyopathy, identified shortly after receiving POEM; this is the only SAE not related to a treatment which resulted in early discontinuation of the study.

For the group of patients treated with PD there were 2 SAEs not related to treatment. One patient was diagnosed with a viral pericarditis, for which they were admitted and treated with NSAIDs. The second patient was diagnosed with a, probably viral, pneumonia; because this SAE occurred shortly after PD, it was doubtful whether it was or was not related to the intervention. Patient required admission and was treated with antibiotics and antivirals.

Section – What you need to know

Background and context: Achalasia patients with persistent or recurrent symptoms after laparoscopic Heller myotomy are most frequently treated with pneumatic dilation. Per-oral endoscopic myotomy is increasingly investigated as rescue therapy; this study aimed to determine the efficacy of per-oral endoscopic myotomy versus pneumatic dilation for patients with persistent or recurrent symptoms after laparoscopic Heller myotomy.

New findings: Per-oral endoscopic myotomy resulted in a significantly higher success rate than pneumatic dilation, respectively 62.2% vs. 26.7%, in achalasia patients with recurrent or persistent symptoms after laparoscopic Heller myotomy.

Limitations: Primary and secondary outcomes were assessed at 1-year follow-up, meaning no conclusions can be drawn for longer-term treatment success, which is important given that achalasia is a lifelong chronic disease. Furthermore, like most endoscopic or surgical studies that evaluate new interventional techniques, patients and caregivers were not blinded to treatment allocation. Lastly, multiple pneumatic dilation sessions might form a potential bias in the comparison to 1 treatment intervention; however, this was done deliberately to optimally reflect routine clinical care in these patients.

Clinical research relevance: Per-oral endoscopic myotomy can be considered as the initial treatment option for achalasia patients with persistent or recurrent symptoms after laparoscopic Heller myotomy.

Basic research relevance: This randomized controlled trial demonstrates that per-oral endoscopic myotomy results in significantly lower Eckardt scores than pneumatic dilation for achalasia patients with persistent or recurrent symptoms after laparoscopic Heller myotomy.

Section – Lay summary

In achalasia patients with persistent or recurrent symptoms after laparoscopic Heller myotomy, per-oral endoscopic myotomy resulted in a significantly higher success rate than pneumatic dilation, with a numerically higher incidence of grade A-B reflux esophagitis.