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Authors

Yadlapati, Rena
Gupta, Samir

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Peroral Endoscopic Myotomy versus Pneumatic Dilation in Achalasia: Dissecting the Randomized Controlled Trial

RENA YADLAPATI,

Department of Clinical Medicine, Division of Gastroenterology & Hepatology, University of California, San Diego, La Jolla, California

SAMIR GUPTA

Department of Clinical Medicine, VA San Diego Healthcare System, Division of Gastroenterology & Moores Cancer Center, University of California, San Diego, San Diego, California

Abstract

Ponds FA, Fockens P, Lei A, et al. Effect of peroral endoscopic myotomy vs pneumatic dilation on symptom severity and treatment outcomes among treatment-naïve patients with achalasia.

First-line treatments for achalasia have historically been limited to laparoscopic Heller myotomy and pneumatic dilation (PD), the latter being the most commonly performed treatment for achalasia worldwide. Ten years ago, per-oral endoscopic myotomy (POEM) was introduced as a novel endoluminal approach for myotomy at the lower esophageal sphincter. Numerous observational cohort studies suggest a higher efficacy of POEM compared with PD for achalasia. However, lack of high-quality data has challenged the clinical adoption of POEM.

Ponds et al conducted the first randomized controlled trial comparing the efficacy of POEM and PD in treatment-naïve achalasia (*JAMA* 2019;322:134–144). The study was performed as a multicenter unblinded randomized controlled trial at 6 hospitals with expertise in achalasia management across the world between September 2012 and July 2015. Adult patients with symptomatic achalasia, meeting standard manometric criteria for achalasia, naïve to treatment (with the exception of Botox injection >3 months prior) were randomized 1:1, stratified by site, to PD or POEM. PD was first performed to 30 mm, and repeated to 35 mm at 3 weeks if not meeting criteria for treatment success. Patients assigned POEM underwent myotomy to a minimum proximal length of 6 cm in the esophagus. Interventions in both arms were performed by proceduralists with experience performing 20 cases of the respective procedure. For both arms, a proton pump inhibitor was prescribed after intervention for 2 weeks. Patients were followed for 2 years, completed questionnaires, and underwent endoscopy, manometry, barium esophagram, and pH impedance testing. Patients who remained symptomatic were considered treatment failures and underwent retreatment; those in the PD arm underwent PD at 40 mm and, if still unsuccessful, POEM, whereas those in the POEM arm underwent a graded PD protocol starting at 30 mm. Although allocation was concealed on study enrollment, once randomization was complete, patients and investigators were unblinded to group assignment. Primary outcome was treatment

success at 2 years, defined by an Eckardt score of ≤ 3 , absence of retreatment, and absence of severe post-treatment complications.

The primary modified intent-to-treat analysis excluding patients who did not undergo assigned treatment included 130 patients in which 66 were randomized to PD and 64 to POEM. Treatment success was 92% for POEM, significantly higher than 54% for PD ($P < .001$) corresponding with a number needed to treat of 2.6. Reflux esophagitis was significantly higher in the POEM arm (41%) compared with the PD arm (7%), with the majority of esophagitis in the POEM arm being mild in severity. There were 2 serious adverse events with PD and none with POEM. An adjusted multivariable regression model did not detect significant differences in secondary outcomes of integrated relaxation pressure or barium column height between arms.

Comment.

POEM is an advanced endoluminal procedure that offers a safe and definitive treatment option for the management of achalasia (Endoscopy 2010;42:265–271). Yet, many questions about the role of POEM compared with historical gold standards of PD and surgical myotomy have limited its clinical uptake. This first of its kind randomized controlled trial comparing POEM and PD is an initial tremendous step to address this void.

The primary finding in this study is that POEM outperforms PD in terms of overall treatment success, measured by the Eckardt score and need for retreatment, at 3 months, 1 year and 2 years. These findings are replicated in post hoc analysis and adjusted regression models. Further, POEM is a relatively safe treatment option with no serious adverse events reported in this study.

Although an overall rigorous well-conducted multicenter randomized controlled study, there are notable limitations that should be considered in interpreting the report. First, the lack of significant differences in physiologic markers of treatment success between the 2 arms is perplexing. For instance, a primary objective of definitive therapy in achalasia is to improve bolus emptying. However, despite a lower rate of treatment success defined by the Eckardt score and need for retreatment, patients in the PD arm had a nonsignificantly lower mean barium column height on esophagram (0 cm) at 2 years compared with patients in the POEM arm (2.3 cm). Although the study was not powered to detect statistical differences in secondary outcomes, these unexpected physiologic patterns question the actual mechanism of symptom response in this study.

Second relates to the study protocol for PD and POEM. Often a criticism of studies evaluating PD is the lack of a standardized PD protocol because proceduralists vary in their choice of initial dilator size and serial dilation practice. In this study, investigators a priori developed a detailed standardized protocol for PD. The PD protocol begins with a 30-mm dilation, which is standard of care, and ends after 35 mm of dilation. In standard practice, patients may be offered dilation to 40 mm. In particular, younger males with achalasia may have thicker lower esophageal sphincter musculature and may require larger dilations (Clin Gastroenterol Hepatol. 2004;2:389–394). Along the same lines, 4 patients in the PD arm

meeting criteria for treatment failure refused additional treatment beyond 30 mm. These factors may overestimate the treatment failure rate with PD than what would be seen in the real-world, and results are not entirely generalizable.

With regard to the POEM protocol, the supplemental documents describe a minimum proximal myotomy length of 6 cm, but do not describe the extent of proximal myotomy length performed. This is particularly relevant to 12 of 18 patients with type III achalasia that were randomized to the POEM arm. The efficacy of extended proximal myotomy tailored to the spastic segment in the esophagus in type III achalasia is well established (Br J Surg 2019;106:332–106341). For this reason, some experts recommend POEM with extended myotomy as the first-line treatment option for type III achalasia if the expertise is available. (Gastroenterology 2017;153:1205–1211). Thus, whether an extended myotomy influenced treatment success in the POEM arm is an important and missing detail.

Third, the lack of blinding risks ascertainment bias and may contribute to overestimation of treatment effect with POEM (Can J Surg 2010;53: 345–348). Although blinding is a critical methodologic feature of randomized controlled trials, the authors of this study provide a strong rationale for the decision to unblind (eg, increased subject risk and resource use in blinding), as is often the case for proceduralbased randomized controlled trials. Nonetheless, superiority of POEM versus PD for subjective but not physiologic outcomes could in part be explained by bias related to inability to blind patients or outcome assessors.

Overall, this rigorous randomized controlled study highlights that POEM is an effective and relatively safe treatment option for achalasia. Despite methodologic limitations, POEM seems to perform better than PD in terms of symptom improvement. As expected, POEM is associated with an increased risk of symptomatic and erosive gastroesophageal reflux disease. The differences in physiologic mechanism of action between PD versus POEM are not clear in this study.

This study adds to the emerging body of literature surrounding POEM and provides the highest level of evidence to date to support the therapeutic role of POEM in treatment naïve achalasia. Results of prior prospective cohort studies report similar success rates of POEM. For instance, the clinical success in the first 100 patients prospectively assessed following POEM was 99% (Surg Endosc 2016;30:4817–426). Although a randomized controlled trial comparing POEM to surgical myotomy is not available, a recent meta-analysis of studies reported a significantly higher success rate with POEM than surgical myotomy in type I achalasia (odds ratio, 2.97; 95% confidence interval, 1.09–8.03) and type III achalasia (odds ratio, 3.50; 95% confidence interval, 1.39–8.77) (Br J Surg 2019;106:332–341).

Thus, POEM does seem to have promise as a definitive treatment approach for achalasia. Centers caring for patients with achalasia should offer POEM as a definitive treatment option for achalasia, if adequate expertise and surgical support are available. Further, clinicians should incorporate POEM into the treatment armamentarium for achalasia and review the efficacy and risks of POEM compared with PD and laparoscopic Heller myotomy in a shared decision-making care model for patients with treatment-naïve achalasia that are candidates for definitive therapy. Remaining gaps that need to be addressed are high-quality

comparative effectiveness studies across all three interventions for achalasia. Further, because POEM is a relatively new therapy, learning curves for procedural technique and long-term outcomes need to be further studied and defined, as does the mechanism by which POEM may achieve superior outcomes to PD. In particular, the risk of gastroesophageal reflux after POEM has tempered enthusiasm for POEM in some centers, and the efficacy in antireflux management of pharmacologic acid suppression and/or endoluminal antireflux interventions after POEM requires clarification. In the end, this study heralds a practice-changing paradigm in which POEM is among 1 of 3 definitive therapies for achalasia, and may conceivably become the new standard therapy.