

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 77165

Title: Peroral endoscopic myotomy versus laparoscopic myotomy and partial fundoplication in esophageal achalasia: a single-center randomized controlled trial

Provenance and peer review: Invited Manuscript; Externally peer reviewed

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Position: Peer Reviewer

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="radio"/>] Anonymous [<input type="radio"/>] Onymous
	Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No

SPECIFIC COMMENTS TO AUTHORS

This is an interesting RCT that compared treatment naive achalasia outcomes in the short term following either POEM or Heller Myotomy with partial fundoplication. The outcomes show that the results are comparable, at least in the short term (up to 1 year) with an increased preponderance for reflux in the POEM group. There are several concepts however that deviate from other studies. Firstly, conventional manometry was used to define pathology and outcome using LES pressure rather than IRP, the most widely used parameter in the literature for studies of POEM. Further, although the timed barium swallow was used as an objective measure of response, in the many (?perhaps the majority), there remained a column of barium retained, rather than complete clearance by 5 minutes. Also all POEM procedures used the long myotomy, with full thickens muscle dissection and undertaken using the posterior approach, all of which studies have suggested might increase risk of reflux, which I appreciate the authors comment on. I have a few comments: 1. In the abstract, there is mention of the 'mega-esophagus' but the study did not separate mega-esophagus specifically so it is not clear why it received specific mention in the abstract 2. Under clinical assessments the authors say: 'Achalasia was classified by clinical subtype, according to the degree of esophageal dilation on the barium esophagogram and esophageal motor activity on EM' Is there any evidence that achalasia can be subtyped used these techniques? Achalasia subtyping is defined based on HRM, all other techniques are presumptions. Further the study does not elaborate on the subtyping and difference between them, so it is not clear how this suggested subtyping impacted 3. Was there any difference in the technical aspects of procedures, outcomes, questionnaire response

etc between those who were found to have Chagas and those who didn't? Only the baseline differences were described. How many Chagas were randomized into each arm?

4. Authors say: 'Treatment success was defined as symptom improvement (≤ 3 -point reduction in the Eckardt score), an LES pressure < 15 mm, and a $> 50\%$ reduction in the height of the barium column at 1 min. Treatment failure was defined as symptom persistence in patients with an Eckardt score ≥ 3 .' Firstly pressure is measured as mmHg, not mm. Secondaly, Achalasia is not a disorder necessarily associated with a high vs low LES pressure, rather it is the relaxation that matters, hence the IRP parameter in HRM. Achalasia can exist with normal LES pressure but requires a nonrelaxing LES pressure gradient. But I appreciate HRM was not available. Can the authors provide evidence that LES pressure <15 mmHg is a good predictor of success/outcome response? Did every patient have repeat EM? I find it surprising that not everyone was agreeable to endoscopy but everyone agreed to have an EM, especially considering the discomfort of the pull through conventional manometry technique. Finally, what evidence is there that $>50\%$ reduction in the height of barium column at 1 minute is a good test for response. Indeed looking at the table, many patients had a retained column of barium at 5 min. Doesn't that suggest hold up and persistent retention? One study the authors might find beneficial to justify their 50% response is: Sanagapalli et al. The timed barium swallow and its relationship to symptoms in achalasia: Analysis of surface area and emptying rate. NGM 2020 5. In this study there is a suggestion that there is an increased preponderance of reflux in POEM. In those who had endoscopy, 1 year post fundoplication, 1 had Grade C esophagitis whilst post POEM, 4 had grade C and 2 grade D esophagitis. We need to be careful about defining reflux in those with grade A (even B) esophagitis as according to the recent Lyon consensus of reflux disease, in Grade A and B there is an overlap with healthy, asymptomatic individuals (Gyawali CP, Kahrilas PJ, Savarino E, et al. Modern diagnosis of GERD: the Lyon consensus. Gut 2018).



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Furthermore most patients with reflux symptoms following POEM commonly respond very well with acid reducing therapy. (Familiari et al Dig Endosc 2016) Many of those with advanced esophagitis were seen at the 6 month follow up. Were these patients not treated with medication? 6. With regards to the increased reflux symptoms risk, please consider commenting on a study by Ponds et al Gut 2021 who assessed reflux symptoms following achalasia therapy. In many cases, the presence of reflux symptoms, objective measures of acid exposure and the presence of esophagitis do not correlate. 7.

Authors say that 'POEM technique was not fully described and standardized until 30 years later'. It has been less than 30 years since POEM was used in humans in 2010. 8.

It is surprising that despite the increased esophagitis risk, there was nearly no regurgitation post POEM on the Eckardt score in table 2 as in most Eckardt was near 0. 9.

Table 5 needs to specify 'cm' 10. Did any have HRM? Has this data been assessed re IRP? Perhaps if there is a large enough cohort of those who had HRM the data should be shared to confirm that results correlate with conventional manometry.

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SPECIFIC COMMENTS TO AUTHORS

The Authors compared in a single center randomized controlled trial (RCT) peroral endoscopic myotomy (POEM) and laparoscopic myotomy with partial fundoplication (LM-PF) in patients suffering from achalasia evaluating their efficacy and other outcome measures, including the occurrence of adverse events. POEM and LM-PF appeared equally effective in improving the symptoms of achalasia and the manometry values with similar length of hospital stay and adverse events, but POEM significantly shortened anesthesia and procedure time, whereas showed the rates of reflux esophagitis significantly higher than LM-PF, despite an improvement of the quality of life in all domains at variance with LM-PF. The design of the study is correct but there are some observation to do in its realization.

ABSTRACT. Last line of Results: the LM-PF results regarding QoL are missing. **Conclusions:** the significantly higher rate of GER in POEM has not been reported.

TEXT **Introduction** The reference 8 is incorrect, because I did not find any article of Winter et al dated 2015 in PubMed. The pages are not numbered. **Materials and methods** The techniques used for the assessment of the postmyotomy results require some observations.

- As the occurrence of gastroesophageal reflux (GER) seems to characterize the difference between the effects of LM-PF and POEM, it is necessary that its evaluation be done with a very reliable technique. The GerdQ does not seem a valid tool for research, all the more in operated achalasic patients, being designed for a family practitioner (ref. 24), being based on subjective symptoms, which sometimes may be fallacious and cannot allow an objective statistical study. The reasons why the Authors chose this technique are reported in the Discussion, where I will explain the inconsistency of them. The Authors

should have chosen 24 h pH monitoring for this purpose, which is able, unlike GerdQ, to provide objective and quantitative data of GER. The 24h pH monitoring technique has been applied alone or in association with other criteria in most studies similar to the present one concerning the problem of GER after myotomy (Benini L. et al Dig Dis Sci. 1996 ;41:365; Repici A et al Gastrointest Endosc. 2018; 87; 934; Huang Z et al Gastrointest Endosc. 2021;93:47; Sanaka MR et al Surg Endosc. 2019 ;33:2284; etc.). Furthermore, the 24h pH monitoring was also used in many articles cited by the Authors concerning the POEM technique (references n. 44-49 and 51). -The use of barium esophagogram to measure the esophago-gastric transit is a rough technique that does not allow a precise evaluation and exposes the patient to radiation doses higher than those of the scintigraphic method, that should have been used. The Authors must give an explanation of their choice. -The conventional esophageal manometry is a still valid method of assessing lower esophageal sphincter pressure (LESP), which is a crucial datum in the assessment of the myotomy efficacy in achalasia. Therefore more details about the equipment and the measurement procedure are needed. Results The Authors should explain why POEM patients, despite having a postmyotomy LESP similar to that of LM-PF, show more reflux. Usually the application of partial fundoplication induces a significant increase of LESP (Chrysos E et al J Am Coll Surg. 2003;197:8; Lindeboom MY et al Dis Esophagus. 2007;20:63), but the LESP values of the two groups turned out not significantly different. I did not find any Adverse events description in the Results regarding both POEM and LM-PF. Tables and Figures The Table 5 and supplementary table 2 titles lack the indication of what the numerical values refer to (cm?) and there is no statistical evaluation. The Table 6 title lacks the indication of what numerical values refer to (LESP? mmHg?) and there is no statistical evaluation. The Figure legends are the same as those reported under Figures. Why this repetition? In the Supplementary Figure 1 what the arrows indicate is missing. Discussion The Discussion is somewhat

disorderly. The observations on results of myotomy of Chagas disease should be placed where the outcomes are reported and the complications should be placed after the results. Why the Authors neglected the articles of Schneider et al 2016 Repici et al 2017 and Sanaka et al 2019 in the comparison of their results with those of other studies? The Authors used the GerdQ tool instead of 24h pH monitoring arguing that the endoesophageal pH can be influenced by lactic acid due to food fermentation caused by chronic retention. This reason may be valid before myotomy, but not after myotomy, which does not allow an important stasis with fermentation and lactic acid generation (Smart HL et al Gut. 1987;28:883). Consequently the presumed presence of lactic acid does not represent a justification for not using the 24 hour pH monitoring. In any case the acid peaks of the refluxes can be easily recognized in the pH tracing (for additional precision, but not necessarily, can be used the pH-impedenziometry). As said previously, the 24 hour pH monitoring has been applied alone or in association with other criteria in most studies concerning the reflux after myotomy. So the Authors must indicate in the Discussion that the lack of an objective evaluation of the GER with 24 h pH monitoring is a significant limitation of the study.