RESPONSE TO REVIEWERS

Dear Dr. Ribeiro,

We are pleased to inform you that, after preview by the Editorial Office and peer review as well as CrossCheck and Google plagiarism detection, we believe that the academic quality, language quality, and ethics of your manuscript (Manuscript NO.: 77165, Randomized Clinical Trial) basically meet the publishing requirements of the *World Journal of Gastroenterology*. As such, we have made the preliminary decision that it is acceptable for publication after your appropriate revision.

Upon our receipt of your revised manuscript, we will send it for re-review. We will then make a final decision on whether to accept the manuscript or not, based upon the reviewers' comments, the quality of the revised manuscript, and the relevant documents.

Please follow the steps outlined below to revise your manuscript to meet the requirements for final acceptance and publication.

Thank you. We followed all requirements as requested.

1 MANUSCRIPT REVISION DEADLINE

We request that you submit your revision in no more than **14 days. Please note that you have only two chances for revising the manuscript**.

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3 SCIENTIFIC QUALITY

Please resolve all issues in the manuscript based on the peer review report and make a point-by-point response to each of the issues raised in the peer review

report. Note, authors must resolve all issues in the manuscript that are raised in the peer-review report(s) and provide point-by-point responses to each of the issues raised in the peer-review report(s); these are listed below for your convenience:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

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.

Thanks for the suggestion. We included this result in the revised article.

Conclusions: the significantly higher rate of GER in POEM has not been reported.

Thanks for the suggestion. We included this result in the revised article.

TEXT

Introduction

The reference 8 is incorrect, because I did not find any article of Winter et al dated 2015 in PubMed.

Reference 8 is correct. This article was published in a non-indexed journal. (Winter H, Shukla R, Elshaer M, Riaz AA. Current management of achalasia - A review. Br J Med Pract. 2015;8(2):a810.).

The pages are not numbered.

We corrected the revised article according to your suggestion and the journal's rules.

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).

Thanks for your comment. We have a different point of view, since the use of the 24-hour pH monitoring to assess gastroesophageal reflux in patients with achalasia, submitted to surgery or the endoscopic method, is criticized for the limitation in the interpretation of its data, due to the process of fermentation that occurs in this specific group of patients, as a result of the non-existent motor activity, providing stasis, fermentation and acidification of the medium. This examination was a reason for discussion prior to the completion of this study, having been chosen not to perform it and greater appreciation of clinical manifestations and endoscopic examinations. However, based on your other comment below in the Discussion part, regarding performing 24-hour pH monitoring after the procedures, we included not performing a 24-hour pH monitoring as a limitation of our study.

"All patients with symptoms and suggestive endoscopic findings of GER received PPI treatment with suspension or maintenance according to the clinical and endoscopic response. A significant limitation of our study was the absence of pHmetry evaluation, which is the main method for GERD evaluation. Prior to our study, we considered that the pHmetry evaluation would be compromised because patients with esophageal achalasia present retention of food residues in the esophageal mucosa and the fermentation of those residues can decrease the intraluminal pH and thus be a confounding factor in the diagnosis of GERD. However, Smart et al. [Smart HL, Foster PN, Evans DF, Slevin B, Atkinson M. Twenty four hour esophageal acidity in achalasia before and after pneumatic dilatation. Gut. 1987 Jul;28(7):883-7] showed that such fermentation would affect only pre-procedure pHmetry, without much influence on the post-procedure pHmetry. "

-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.

Thanks for your comment. We agree with the indication of scintigraphy for this purpose, however, like several centers, mainly in less developed countries, we do not have it available for all studies. The timed study of esophageal emptying is extremely useful and a predictor of poor results. Also, it is widely used in many centers and in different continents. We are convinced of the real benefit of this technique.

-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.

Thanks for your comment. We have included the details of the equipment and how we performed the procedure in the revised article.
"To perform conventional EM, we used an eight-channel computerized polygraph under pneumohydraulic capillary infusion at a flow rate of 0.6 ml/min/channel. Preparation was required with a 12-hour fast and suspension of medications that alter esophageal motility. The technique consists of passing a probe through the nostril and checking the position in the stomach through deep inspiration. With the patient in the supine position, the probe is pulled centimeter by centimeter to measure the mean respiratory pressure and pressure inversion point, and then one of the channels is positioned distal to 3 cm from the upper edge of the lower esophageal sphincter and the other channels are distant 5cm apart. Finally, the catheter is pulled up to the upper esophageal sphincter.
Through the average of the four distal radial channels of the conventional manometry catheter, the maximum expiratory pressure (MEP) was identified, which best represents the pressure of the LES pressure itself."

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.

It must be understood that LES pressure is one of the containment factors. The fact of being elevated is not synonymous with containment of gastroesophageal reflux. In POEM, regardless of the LES pressure values, we have the esophagogastric transition permanently open, favoring reflux and, as there is a clearance deficit, we have stasis, fermentation, interfering with the pH of the organ. We have included this matter in the revised article (Discussion section) as per your suggestion.

"We consider that patients undergoing POEM have a wider esophagogastric transition that favors a higher rate of gastroesophageal reflux compared to LM-PF, despite similar LES pressure between the groups. Werner et al.[43] also showed more gastroesophageal reflux in patients undergoing POEM despite no difference in manometry compared to LM-PF."

I did not find any Adverse events description in the Results regarding both POEM and LM-PF.

Adverse events were described both in the text of the results and in the table, see excerpts below:

"There was no statistical difference between the two groups regarding the rate of AEs (P = 0.605). The relevant complications observed in the immediate postprocedural period included empyema requiring thoracostomy in one (5%) of the LM-PF patients, and inadvertent intraoperative mucosal damage in three

(15%) of the POEM patients (treated with endoscopic clipping). The clinical outcomes were favorable in all patients."

	Group			
Variable	**Total (*N* = 40)**	**LM-PF (*n* = 20)**	**POEM (*n* = 20)**	***P***
Adverse events, *n* (%)	4 (10.0)	1 (5.0)	3 (15.0)	0.605*

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.

Thank you very much for the observation. Numerical values are in centimeters (corrected in the revised article) and the statistical evaluation was included in the revised article.

"Table 5 shows the results of the barium esophagogram. In both groups, the heights of the barium column at 1 and 5 min were significantly lower at 1, 6, and 12 months than at baseline ($P < 0.001$). There was no statistical difference between the two groups regarding the barium column height values at 1 and 5 minutes in the follow-up periods (intent-to-treat analysis: p= 0.429 and 0.773; per-protocol analysis: p=0.505 and 0.922)."

The Table 6 title lacks the indication of what numerical values refer to (LESP? mmHg?) and there is no statistical evaluation.

Thank you for your comments. Table 6 refers to the LESP values, being graded in mmHg (corrected in the revised article). The statistical evaluation is also in the revised manuscript.

"In both groups, the maximal expiratory pressure (MEP) values were significantly lower at 6 and 12 months than at baseline (Table 6). There was no statistical difference between the two groups at either of those time points (intention-to-treat analysis: P = 0.848)."

The Figure legends are the same as those reported under Figures. Why this repetition?

Thank you very much for the observation. We corrected it in the revised article.

In the Supplementary Figure 1 what the arrows indicate is missing.

Thank you very much for the observation. We corrected it in the revised article.

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.

Thank you for your comment. We report the results of a study comparing POEM in idiopathic and Chagas disease achalasia as we believe that such results would be more related to epidemiological data (high prevalence of Chagas disease in Brazil), which is why it is in the first paragraph of the discussion; complications are included in results because it was one of the outcomes used in our study, with a paragraph below the outcomes we deem most important being discussed.

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?

Thanks a lot for the suggestion. The cited articles were not neglected. They were not included because they had some limitations, as described below:

1. The study by Schneider et al, 2016 involves an analysis of 2 (two) cohorts of patients undergoing treatment of achalasia with POEM vs Heller myotomy. The groups are not uniform, the follow-up time is very different, so the results are open to criticism.
2. This article by Repici et al, 2018 includes only retrospective studies, with a high rate of heterogeneity, non-homogeneous groups, like other studies of systematic reviews, more recent and cited in our text.
3. The article by Sanaka et al 2019 includes non-homogeneous groups in which proportionality interferes with the interpretation of data, as well as previous procedures performed in patients undergoing POEM. Many of these patients had undergone Heller's surgery. There is a very important selection bias. The fact that acid exposure time was high in both groups in this study is due to the fermentation present in patients with achalasia.
Because of these factors, and due to the reference and text limit of the journal's rules, we chose to include the articles that we considered most relevant.

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.

Thanks for your comment. The GerdQ tool was used as a clinical evaluation criterion. It was never used as a substitute for the 24-hour pH-metry test. In one of the comments above, we mentioned the issue of not performing 24-hour pHmetry. Following your recommendation, we have included this topic as a limitation in the revised article.

"All patients with symptoms and suggestive endoscopic findings of GER received PPI treatment with suspension or maintenance according to the clinical and endoscopic response. A significant limitation of our study was the absence of pHmetry evaluation, which is the main method for GERD evaluation. Prior to our study, we considered that the pHmetry evaluation would be compromised because patients with esophageal achalasia present retention of food residues in the esophageal mucosa and the fermentation of those residues can decrease the intraluminal pH and thus be a confounding factor in the diagnosis of GERD. However, Smart et al. [Smart HL, Foster PN, Evans DF, Slevin B, Atkinson M. Twenty four hour esophageal acidity in achalasia before and after pneumatic dilatation. Gut. 1987 Jul;28(7):883-7] showed that such fermentation would affect only pre-procedure pHmetry, without much influence on the post-procedure pHmetry."

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

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.

Thank you for your valuable comments. Below you can check our answers based on your suggestions.

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

Thanks for your comment. We made the correction in the revised article following your suggestion.

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

Thanks for your valuable comment. We agree. We made the correction in the revised article as per your suggestion.

"Although achalasia subtyping is defined based on HRM, in this study, the achalasia subtype was evaluated according to the degree of esophageal dilation

on the barium esophagogram and esophageal motor activity on EM or HRM. Given that Chagas disease, which often involves the esophagus, is common in Brazil, all the patients were screened for anti-*Trypanosoma cruzi* antibodies by enzyme-linked immunosorbent assay and indirect immunofluorescence.

Weight loss, dysphagia, and pain were assessed before the procedure, as well as at 6 and 12 months after the procedure, by using the Eckardt score. Patients with an Eckardt score ≥ 3 were categorized as symptomatic.

The clinical evaluation of gastroesophageal reflux (GER) and the diagnosis of gastroesophageal reflux disease (GERD) was based on the application of the Gastroesophageal Reflux Disease Questionnaire (GerdQ)[24] (Supplementary Chart 1)."

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?

Thank you for your valuable comment. In our study (22.5%) of 40 patients (five in the POEM group and four in the LM-PF group) tested positive for anti-Trypanosoma cruzi antibodies, indicating nine exposures to Chagas disease. (as described in Table 1). In a study published in 2020 (Farias GFA et al. Endosc Int Open. 2020 Apr;8(4):E506-E512. doi: 10.1055/a-1035-9288. Epub 2020 Mar 23. Peroral endoscopic myotomy (POEM): a comparative study between Chagasic and idiopathic achalasia) there was no difference in the results and technical aspect comparing POEM in idiopathic and chagasic achalasia. This Discussion was included in the revised article.

1. 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.

It was a typing error. We made the correction in the revised article. Thanks for the observation.

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<15mmHg is a good predictor of success/outcome response?

Some previously published studies show that LES pressure < 15mmHg after treatment for achalasia is a good predictor of success/outcome. Below are the references of these studies:

- Müller M, Eckardt AJ, Wehrmann T. Endoscopic approach to achalasia. World J Gastrointest Endosc. 2013 Aug 16;5(8):379-90.
- Müller M, Keck C, Eckardt AJ, Werling S, Wehrmann T, König J, Gockel I. Outcomes of pneumatic dilation in achalasia: Extended follow-up of more than 25 years with a focus on manometric subtypes. J Gastroenterol Hepatol. 2018 May;33(5):1067-1074
- Ghoshal UC, Rangan M. A review of factors predicting outcome of pneumatic dilation in patients with achalasia cardia.J Neurogastroenterol Motil 2011; 17: 9-13.

We did include these references in the revised version to clarify this information for readers.

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.

In our institution, we did not have high-resolution manometry available. We performed conventional manometry and parameters available in the literature are adopted at our university.
Regarding patients with repeated EM, it was not easy to convince patients to undergo a new manometry test, however we were successful. We believe that the greatest loss of endoscopic follow-up occurred due to the need for sedation, absence from work activities and the need for a companion. However, we agree that manometry is more uncomfortable than upper gastrointestinal endoscopy.

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

Thank you for your valuable suggestion. We did include this reference in the revised version of the manuscript.

"Sanagapalli S et al. showed an association of significant improvement in symptoms when there is a mean reduction in the residual barium column height by about 53% (Sanagapalli S, Plumb A, Maynard J, Leong RW, Sweis R. The timed barium swallow and its relationship to symptoms in achalasia: Analysis of surface area and emptying rate. Neurogastroenterol Motil. 2020 Dec;32(12):e13928.)."

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). 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?

Thank you for your valuable comment. Because pHmetry was not performed in our study, we defined patients with reflux in our study according to endoscopic findings and symptoms. We performed treatment with PPIs based on endoscopic findings and symptoms of the patients, with suspension or continuity of treatment depending on the clinical and endoscopic response. We included this discussion in our revised manuscript based on your comment.
"All patients with symptoms and suggestive endoscopic findings of GER received PPI treatment with suspension or maintenance according to the clinical and endoscopic response. A significant limitation of our study was the absence of pHmetry evaluation, which is the main method for GERD evaluation. Prior to our study, we considered that the pHmetry evaluation would be compromised because patients with esophageal achalasia present retention of food residues in the esophageal mucosa and the fermentation of those residues can decrease the intraluminal pH and thus be a confounding factor in the diagnosis of GERD. However, Smart et al. [Smart HL, Foster PN, Evans DF, Slevin B, Atkinson M. Twenty four hour esophageal acidity in achalasia before and after pneumatic dilatation. Gut. 1987 Jul;28(7):883-7] showed that such fermentation would affect only pre-procedure pHmetry, without much influence on the post-procedure pHmetry. "

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.

Thank you for your valuable comment. We included this discussion in our revised manuscript based on your comment.

"Despite not including patients undergoing POEM, a recent study [Ponds FA, Oors JM, Smout AJPM, Bredenoord AJ. Reflux symptoms and oesophageal acidification in treated achalasia patients are often not reflux related. Gut. 2021 Jan;70(1):30-39.] showed that achalasia patients with post-treatment reflux symptoms demonstrate esophageal hypersensitivity to chemical and mechanical stimuli, which may determine symptom generation."

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.

Thanks for the comment. Although little commented, the first publication regarding the use of the endoscopic myotomy technique was described by Ortega JA, Madureri V, Perez L. Endoscopic myotomy in the treatment of achalasia. Gastrointest Endosc. 1980;26(1):8-10 in 1980, but the technique used was not reproduced and was eventually abandoned. Based on your comment, we have included this information more clearly in the revised article.

"In the first study involving the use of endoscopic myotomy[21], conducted in 1980, all 17 of the patients in the sample showed symptom improvement.

Although, technical improvements proposed by Inoue et al. in 2010 and several cohort studies comparing POEM and LM-PF [20,32-42] over the last decade have proved its safety and efficacy in the management of achalasia, the POEM technique is still not fully standardized [22].”

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.

Thanks for the comment. This is really an interesting finding from our study. We believe that there was no regurgitation due to an improvement in esophageal emptying.

9. Table 5 needs to specify ‘cm’

Thank you for your correction. We made the correction in the revised version of the manuscript.

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.

Thanks for the comment. It would really be an interesting piece of data, but unfortunately, we did not have the High-Resolution Manometry test available when the protocol was carried out. HRM was recently acquired at our university.

4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Authors are requested to send their revised manuscript to a professional English language editing company or a native English-speaking expert to polish the manuscript further. When the authors submit the subsequent polished manuscript to us, they must provide a new language certificate along with the manuscript.

Once this step is completed, the manuscript will be quickly accepted and published online. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240.

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