World Journal of Gastroenterology

Re: *Qu CY & Zhang FY et al.* "**Endoscopic Polidocanol Foam Sclerobanding in the Treatment of grade II-III Internal Hemorrhoids: A Prospective, Multi-center, Randomized Study.**"

Dear reviewer,

Thank you very much for arranging a timely review of our manuscript. We have carefully evaluated the reviewers' comments and professional suggestions, revising the manuscript accordingly. Based on these suggestions, we have made corrected modifications, all of which are highlighted in yellow and underlined to facilitate their identification. We believe these changes can help to improve academic rigor of our manuscript, and hope that it will now be attractive to the readers of *WJG*.

Our specific point-by-point responses to the reviewers' comments are listed as follows:

REVIEWERS' COMMENTS TO AUTHOR:

Reviewer: #1

This is an interesting paper that has potential to be published. The title of the paper should be "A multicenter comparison of Endoscopic rubber band ligation vs poliocanol foam sclerotherapy for stage II/III haemorrhoids" The paper however needs to be edited for English grammar and wordings. There are many words which are used wrongly and therefore convey the wrong meanings. I quote here only a few of the sentences which need to be corrected. But there are many other sentences and words which need to be corrected in this manuscript thus: "With the development of gastroscope or flexible colonoscope, the use of retroflex endoscopic RBL (ERBL) could provide better maneuverability, photographic documentation, and more ligations performance" "With the development of flexible endoscopy, the use of retroflex endoscopic RBL (ERBL) will provide better maneuverability, photographic documentation, as well as better performance of haemorrhoidal

ligation." "However, to date, no retroflex endoscopy sclerobanding has been reported". "However, to date, no significant series of retroflex endoscopy sclerobanding had been reported". "The primary aim was a superiority comparison of 12-months prolapse recurrence in the EFSB vs. ERBL group" "The primary aim was a comparison of the difference at the prolapse recurrence between EFSB vs. ERBL groups at 12 months". "Randomization was performed after completing the colonoscopy and decided to conduct the endoscopy treatment of internal hemorrhoids". "Randomization was only performed after completing the colonoscopy and having decided that endoscopy treatment of internal hemorrhoids was necessary". I have not quoted many other examples from this paper which need editorial assistance to correct.

Response: We appreciate the valuable tips provided by the reviewer.

In the manuscript, we firstly evaluated the therapeutic effect and safety of cap-assisted endoscopic polidocanol foam sclerobanding for grade II-III internal hemorrhoids, which has not been previously reported. From our point of view, the current title fits the aim and contents of the study, conveying the scope and nature, and are able to highlight these favorable treatment outcomes.

After thorough discussion and analysis of the suggestions for the article title put forward by the reviewer, we have prepared an alternate title, ***"Prospective, Multi-center and Randomized Comparison of Endoscopic Polidocanol Foam Sclerobanding vs. Rubber Bnad Ligation for Grade II-III Internal Hemorrhoids"***.

Both the current title and the alternate title are appropriate for this manuscript. We can change the title if necessary. Once you have better suggestion, please do not hesitate to put forward, and we will actively adopt it.

When it comes to language errors, we have addressed these mistakes highlighted by the reviewer and made necessary corrections, which are highlighted in yellow. Additionally, we have engaged a language editor to meticulously proofread the grammar and diction of the article once more, ensuring its fluency and alignment with the standards of the journal.

Reviewer: 2

1. This is a nice RCT on a clinically relevant topic. Many shortcomings have already been acknowledged in the study's limitation. I have few comments/suggestion to help the manuscript.

Response: Thanks for reviewer's recognition of this manuscript.

2. Why the median (IQR) rather than the mean (SD) was used to express all the continuous variables. Continuous variables with a normal distribution are typically reported as mean (SD), and the t-test should be used for their comparison rather than the Mann–Whitney U.

Response: We appreciate the reviewer's insightful suggestion. The continuous variables in this manuscript are various evaluation indexes, including HHS and VAS. Hemorrhoid severity score (HSS) is a newly evaluation system comprising five items scored between 0 and 3 (0 indicating best and 3 worst health status) [1-2]. A total score is obtained by summing the answers to each item. Lower scores indicate better hemorrhoidal health. Something like that, the Vaizey incontinence score questionnaire (VAS) is a seven-item measure calculated by summing responses across seven items about fecal incontinence[3]. Decimals may appear while using mean (SD) to express scores, which might be irrelevant because no decimals would appear in reality. That is why the data were presented as median (IQR) rather than the mean (SD). Statistical analysis showed that HSS and VAS scores showed skewed distribution, so that the Mann-Whitney U, rather than the t-test was used.

Besides, we feel sorry for our carelessness in mistakenly writing *HSS* as *HHS*. In our resubmitted manuscript, the typo is revised.

3. Was there not a technical failure in the institution of intended therapy in any group? The authors did note that 3.1% of individuals in the ERBL group had the rubber band come off during surgery. Why didn't that occur in the EFSB group?

Response: Thanks for the reviewer's attention. Due to their convenient operation, endoscopic sclerotherapy and rubber band ligation can be easily mastered by experienced endoscopists. No technical failures were reported in any group.

In the ERBL group, 3.1% of individuals experienced rubber band detachment during the operation, a phenomenon not observed in the EFSB group. As we mentioned in the manuscript, injection of sclerosing agents could lift the mucosa and facilitate ligation, which may attribute to reduce the risk of rubber band detachment.

4. An intention-to-treat analysis would yield a more desirable result.

Response: As suggested by the reviewer, intention-to-treat analysis enables investigators to draw accurate (unbiased) conclusions regarding the effectiveness of an intervention. In comparison to "per-protocol" analysis, intention-to-treat analysis preserves the benefits of randomization, which cannot be assumed when using other methods of analysis[4].

In the manuscript, 5 patients were lost to follow-up after completing treatment and discharge, resulting in incomplete peri-operative and point-in-time follow-up data. As a result, no data was available for analysis, leading to their exclusion from the statistical scope. However, it should be noted that inclusion of baseline and treatment data for these patients aligns with the conclusions drawn in the manuscript. If necessary, we are able to provide this additional data. Furthermore, **we will make revisions to Figure 3** in order to eliminate any potential ambiguity and we sincerely appreciate your valuable suggestion.

5. Did patients with or without a history of bleeding respond differently to treatment?

Response: We appreciate the reviewer's attention to this issue. Among patients with grade II/III, the majority had a history of bleeding. The preoperative bleeding symptoms were present in 85% (n=83) of the EFSB group and 87% (n=84) of the ERBL group, respectively. During test design and patient enrollment, Goligher's classification was utilized for categorizing the severity of internal hemorrhoids. The traditional classification primarily focuses on the degree of prolapse, overlooking other clinical symptoms such as bleeding, which represents a notable limitation. Upon reevaluation of endoscopic features, including the quantity and diameter of hemorrhoid nucleus, presence of a red sign, and other relevant endoscopic characteristics, and subsequent multivariate analysis, it was determined that preoperative hemorrhoid diameter and the presence of red signs were significantly

associated with recurrence. Therefore, it is imperative to consider different treatment modalities prior to surgery. Further detailed data will be presented in a separate manuscript.

6. Did any patients experience any septic problems after receiving therapy for haemorrhoids?

Response: Thank you for the inquiry. Perianal abscess is a known complication of sclerotherapy. In our clinical trial (XHEC-C-2020-003-1), two cases of perianal abscess were reported, one of which involved the use of high concentration (30 mg/mL) sclerosing agents and the other had a history of postoperative chemotherapy for lung tumor. It is important to note that neoplastic diseases were defined as exclusion criteria in this manuscript. Additionally, all individuals included in the manuscript received treatment with 10 mg/mL foaming agents. As a result, none of the 195 enrolled patients developed abscesses.

We are grateful for the careful review and invaluable feedback provided by the reviewers, all of which helped us to significantly improve our revised manuscript. Once again, thank you very much for your comments and suggestions. We look forward to the opportunity to improve our manuscript in response to their guidance.

Yours sincerely

Chun-Ying Qu & Fei-Yu Zhang
May. 28th, 2024
Department of Gastroenterology & Endoscopy, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200092, Shanghai, China

Reference to reply:

[1] Lee MJ, Morgan J, Watson AJM, Jones GL, Brown SR. A validated severity score for haemorrhoids as an essential prerequisite for future haemorrhoid trials. Tech Coloproctol 2019; 23(1): 33-41 [PMID: 30725242 PMCID: PMC6394714 DOI: 10.1007/s10151-019-01936-9]

[2] Nyström PO, Qvist N, Raahave D, Lindsey I, Mortensen N. Stapled or Open Pile Procedure (STOPP) trial study group. Randomized clinical trial of symptom control after stapled anopexy or diathermy excision for haemorrhoid prolapse. Br J Surg. 2010;97(2):167-176. [PMID: 20035531 DOI:10.1002/bjs.6804]
[3] Vaizey CJ, Carapeti E, Cahill JA, Kamm MA. Prospective comparison of faecal incontinence grading systems. Gut. 1999;44(1):77-80. [PMID: 9862829 PMCID: PMC1760067 DOI:10.1136/gut.44.1.77]
[4] McCoy CE. Understanding the Intention-to-treat Principle in Randomized Controlled Trials. West J Emerg Med. 2017;18(6):1075-1078. [PMID: 29085540 PMCID: PMC5654877 DOI:10.5811/westjem.2017.8.35985]