

Dear Dr. Na Ma, dear members of the Editorial Board,

We thank the Editors and the Reviewers for their careful evaluation of our work. The manuscript has been thoroughly modified in light of these comments. We feel that we are now able to submit an improved version of the paper on our prospective study and hope that the revised manuscript will now be suitable for publication in the World Journal of Gastrointestinal Surgery.

Please note that due to absences of co-authors some of signatures for the copyright license agreement are still missing. We will provide the signatures as soon as possible and apologize for the inconvenience. We also noted that an Audio core tip is required for the revised version. Unfortunately, we did not find instructions what exactly is needed here and kindly ask for guidance.

We are looking forward to a constructive reviewing process.

Best regards



Benjamin Misselwitz

On behalf of the co-authors

Reviewer #1: Specific Comments to Authors: In this prospective study, the authors sought to determine the efficacy of a new treatment of perianal fistula disease for which they term “fistulodesis”, which involved curettage of the fistula tract, flushing the tract with acetylcysteine and doxycycline, suture of the inner fistula opening, fibrin glue instillation, and closure of the outer fistula opening. Both Crohn’s disease and non-Crohn’s disease patients were included. Patients were followed for at least 24 weeks. Unfortunately, the procedure was successful in only 30% of patients. There was a trend towards improvement in Crohn’s disease patients, but sample size is limited. Although the findings of the study do not support the routine use of “fistulodesis”, I applaud the authors in trying to solve this difficult to manage problem for both the patient and the surgeon. Both positive and negative studies should be reported in the literature to allow evidence-based surgery. Overall, the study was well designed and the manuscript is well written. The authors comment on the limitations of the study including a small sample size. I think it would be informative to address the following issues:

(1) What prior fistula surgeries were performed? Were they setons only? LIFT? Flap?

Response: We agree with the reviewer, fistula surgery prior to the participation in our study is of crucial importance and could potentially impact on the success of any fistula treatment. In light of the reviewer's comments we now added the requested information on page 9, lines 17-24 of the revised manuscript.

(2) Of the patients that failed, did they go on to have additional surgeries? If so, did they heal?

Response: We are grateful to the reviewer for this comment. All information regarding fistula surgery after failed fistulodesis and successful subsequent fistula closure in some patients was added on page 10, lines 7-13.

(3) It would be of value to include discussion in discussion section prior literature regarding the use of using acetylcysteine and doxycycline (or lack thereof).

Response: We agree with the reviewer. We did not find literature comparing the impact of acetylcysteine and/ or doxycycline on fistula closure. However, we now provide more rational regarding the use of both drugs in the "Methods" section. Acetylcysteine has been used for the cure of a gastro-pancreatic fistula (compare page 7, lines 9-11 of the revised manuscript) and as a mucolytic in many settings (page 7, line 9). Also, literature on the prior use of doxycycline in pleurodesis was supplemented on page 7, line 12 and its benefit when applied for closure of lymphatic fistulae is discussed (page 7, lines 12-13).

(4) Comment which type of suture was used to close the internal and external openings during the procedure.

Response: We agree, a Z-suture technique has been used. This is now explained on page 7, lines 13-14.

(5) Include all p-values in the tables even if not significant.

Response: We agree, all non-significant p-values were added into our tables (see new Table 1 and new Supplementary Table 1).

(1) Science editor: 1 Scientific quality: The manuscript describes a prospective study of the pilot study of a novel minimally invasive surgical and medical approach for closure of perianal fistulae. The topic is within the scope of the WJGS. (1) Classification: Grade C; (2) Summary of the Peer-Review Report: The study was well designed and the manuscript is well written. However, the authors comment on the limitations of the study including a small sample size. The questions raised by the reviewer should be answered; and (3) Format: There are 2 tables and 1 figure. A total of 32 references are cited, including 10 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade A. 3 Academic

norms and rules: The authors provided the Biostatistics Review Certificate, the Clinical Trial Registration Statement, the CONSORT 2010 Statement, and the Institutional Review Board Approval Form. Written informed consent was waived. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The topic has not previously been published in the WJGS. 5 Issues raised:

(1) The “Author Contributions” section is missing. Please provide the author contributions.

Response: *We agree, an “author contributions” section was added (page 1, line 21 until page 2, line 6).*

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response: *We agree, all graphs were rearranged using PowerPoint and submitted as a separate file.*

(3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.

Response: *We adapted all of the cited references as recommended, adding the PMID and DOI citation numbers and listed the names of all authors.*

(4) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text.

Response: *We agree and provided an “Article Highlights” section.*

6 Re-Review: Required. 7 Recommendation: Conditional acceptance.

(2) Editorial office director: I have checked the comments written by the science editor. The author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author’s name, with no spaces.

Response: *The reference numbers were adapted as requested.*

(3) Company editor-in-chief: I have reviewed the Peer-Review Report, the full text of the manuscript and the relevant ethics documents, all of which have met the basic publishing requirements, and the manuscript is conditionally accepted with major revisions. I have sent

the manuscript to the author(s) for its revision according to the Peer-Review Report and the Criteria for Manuscript Revision by Authors. Before final acceptance, authors need to correct the issues raised by the editor to meet the publishing requirements.

Response: *We carefully revised our manuscript, and we would like to thank the editor-in-chief for the constructive comments and the appreciation of our work.*