

November 14, 2019

Dear Editor-in-Chief:

Thank you for inviting us to submit a revised draft of our manuscript entitled, “**Novel zinc alloys for biodegradable surgical staples**” to *World Journal of Clinical Cases*. We appreciate the time and effort that you and each of the reviewers have dedicated to providing insightful feedback on ways to strengthen our paper.

Thus, it is with great pleasure that we resubmit our article for further consideration. We have incorporated changes that reflect the detailed suggestions you have graciously provided. We also hope that our edits and the responses we provide below satisfactorily address all the issues and concerns you and the reviewers have noted.

To facilitate your review of our revisions, our point-by-point responses to the questions and comments delivered in your letter are presented below.

Reviewer code: 02553318

We highly appreciate the reviewer's comment.

We are very pleased that our research is highly appreciated.

We were encouraged to submit our paper to *World Journal of Clinical Cases*, the appropriate journal for our paper. We are glad to resubmit our paper to *World Journal of Clinical Cases*.

Reviewer code: 00058696

We wish to thank the reviewer for these comments.

1) There is no case-control study because the frequency of complications is not high. However, such complications can require re-operations. We do agree that we must consider these complications and pursue better treatment. Furthermore, we do believe that the development of biodegradable staples is highly desired; however, in accordance with the reviewer's comment on the level of evidence, we have removed the word 'highly' (p. 5, line 120).

2) As the reviewer pointed out, inflammatory cell infiltrates were not seen around Ti alloy staples in our study. However, there is a study on inflammatory infiltrate being present mostly in Ti.

Degidi M, Artese L, Scarano A, Perrotti V, Gehrke P, Piattelli A. Inflammatory infiltrate, microvessel density, nitric oxide synthase expression, vascular endothelial growth factor expression, and proliferative activity in peri-implant soft tissues around titanium and zirconium oxide healing caps. *J Periodontol* 2006; 77(1): 73-80. [DOI: 10.1902/jop.2006.77.1.73]

Although Ti is nonbiodegradable and generally inert, there is also a study that shows that Ti can induce clinically relevant hypersensitivity in patients who are chronically exposed to Ti.

Müller K, Valentine-Thon E. Hypersensitivity to titanium: clinical and laboratory evidence. *Neuro Endocrinol Lett* 2006; Suppl 1: 31-5. [PMID: 17261997]

We have cited these in the text (p. 5, line 120) and added them to the references.

3) P values from comparison of corrosion rates of HBSS to FeSSIF are as follows.

Zn alloy staple 1; $p < 0.001$, Zn alloy staple 2; $p < 0.001$, Zn alloy staple 3; $p < 0.001$.

We have added this text to the Results section (p. 11, lines 316–317).

We have also added the following text to the Methods section (p. 10, lines 276-278): The statistical significance of the difference in the corrosion rates between FeSSIF and HBSS was analyzed using the *t*-test.

Final sentence: “The lack of corrosion products on the staple immersed in FeSSIF shows that the component elements eluted as ions.”; We mean that component elements eluted as ions without creating any corrosion products.

4) In accordance with the reviewer's comment, we analyzed the pathology slides again.

Although the inflammatory cell infiltrations around Zn alloy staples at one week after surgery were minimal, those after 4–12 weeks post-surgery were mild-to-moderate. They were not severe; therefore, they are considered to have no adverse effect on local safety. Long-term evaluation is necessary in the future.

We have removed “mild” (p. 14, line 418, p. 33, line 624).

We have added the following text to the Results section (p. 12, lines 350–355):

One week after surgery, minimal inflammatory cell infiltrations—mostly segmented neutrophils and lymphocytes—were localized around only the Zn alloy staples. After 4–12 weeks post-surgery, mild-to-moderate inflammatory infiltrates, composed of eosinophils, lymphocytes, and macrophages, were observed around the Zn alloy staples, along with foreign body giant cells and/or phagocytosis.

Accordingly, the discussion has also been modified (p. 14, lines 416-422) as follows.

Before revision: In addition to systemic biocompatibility, Zn alloy staples have good local biocompatibility; histopathological analysis revealed mild inflammatory reactions around the Zn alloys staples.

After revision: In terms of local biocompatibility, histopathological analysis revealed no severe inflammatory reactions around the Zn alloy staples. Zn alloy staples are considered to have no adverse effect on local safety; nevertheless, long-term evaluation is necessary in the future.

5) We agree and have changed “A simple calculation reveals” to “A simple calculation assuming a stable rate of degradation reveals” (p. 13, line391).

We agree that this point requires clarification and have added the following text to the Discussion (p. 15, lines 433-437): Foreign matter that remains in a living body for a long time runs the risk of causing allergic/foreign-body reactions, adhesion, or other adverse effects. Therefore, in this respect, the use of a biodegradable Zn alloy staple is considered to be less risky than the use of a Ti alloy staple.

Minor Issue: Figure 1 is not needed.

As requested, we have remove Figure 1 from the revised draft.

Thank you again for giving us the opportunity to strengthen our manuscript with your invaluable comments and queries. We have worked hard to incorporate your feedback and hope that these revisions have now made our submission acceptable for publication.

Sincerely,

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