

Peer Review File

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Reviewer A

This is a narrative review about postoperative bleeding after gastric ESD, that is still a big clinical problem. This review covers many kinds of information, however, there are some concerns to be addressed.

Major points

1. There are many papers about postoperative bleeding after gastric ESD including small number and large number of cases. In this review, both are treated in the same way. Large scale study should be weighed more. How about providing some tables for some topics, such as location, anticoagulants, closure, sealing and so on.

Reply 1.

Thanks for the reviewer's constructive suggestion. We added these tables which are very helpful for the message deliveries (Page 6, 11, 14, 16). The tables suppose to be at the end of the manuscript. However, the endnotes would confuse the order of the references. We therefore, inserted the tables into the text.

Yoshio's (41) paper on anticoagulants is very complicated. it not only compared DOACs and warfarin, but also warfarin with HBT vs warfarin without HBT, DOCA with HBT vs DOCA without HBT. To avoid confusing the readers, we just included the data of comparison between DOACs and warfarin in table 2.

2. Especially in the section of anticoagulants, most of the manuscript were with small number of cases and only some of them were with large number. Please focus on the manuscript with large number.

Reply 2.

Thanks for the reviewer's comment. We added Furuhata's study which enrolled 1781 cases.

3. Although authors described about low molecular weight heparin by subcutaneous injection, most of the studies uses unfractionated heparin intravenously. Are their influences different? I do not know much about the influence of low molecular weight heparin for post ESD bleeding.

Reply 3.

The reviewer is right, most of the studies uses unfractionated heparin intravenously. Compared with unfractionated heparin, Low molecular weight heparin (LMWH) has the same anticoagulation effect, less side effect, less frequency of bleeding, does not

require APTT monitoring, can be injected subcutaneously and therefore, it is more convenient and safer. We use LMWH in our clinical practice. There is no comparison of these two different heparins in the literature of post-ESD bleeding. LMWH is more expensive and therefore, is not covered by health care in some countries, like Japan, which might be the reason why most publications used unfractionated heparin.

4. Because authors described about antithrombotic therapy much, why not describing the frequency of thrombotic events.

Reply 4. The reviewer is right. We added this content on page 8.

5. About the second look endoscopy, authors should include at least following RCT. There are some more study.

Mochizuki S, Uedo N, Oda I, et al. Scheduled second-look endoscopy is not recommended after endoscopic submucosal dissection for gastric neoplasms (the SAFE trial): a multicentre prospective randomised controlled non-inferiority trial. *Gut*. 2015 Mar;64(3):397-405.

Reply 5. As per the reviewer's comment, we added more in detail on second-look endoscopy which include Mochizuki's RCT. Page 20.

6. About the closure section, authors should separately discuss the closure with endoloop and endoclips and closure by suturing.

Reply 6. As per the reviewer's comment, we discussed the closure methods separately. Page 13.

Minor points

7. About the description of dabigatran, prodrug converted to active dabigatran not only in the liver and the plasma but digestive tracts. Thus, inactive prodrug of dabigatran pass though the stomach, although other DOACs come to the stomach in active form. These different effect of DOACs were confirmed by ref 23.

Reply 7: "digestive tracts" was added. Page 9.

8. I think description of ref 36 is appropriate, because this manuscript includes not only gastric ESD but colon polypectomy which postoperative bleeding rate is much lower than gastric ESD.

Reply 8: thanks for the reviewer's vigilant eyes, the pertinent content was modified. Page 10

9. I think there is no description about ref 42, because all sentences in the paragraph are about ref 13.

Reply 9. As per the reviewer's comment, we summarized Choe's study and compared ref. 42 to ref. 13. Page 12

10. The word "Lesion closure" and "lesion shielding" are inappropriate, because we close or shield post ESD ulcer.

Reply 10. As per the reviewer's comment, we substituted ESD ulcer for lesion in subtitles. However, both lesion and ulcer were used in the literature (Mochizuki's paper PMID: 2530185 is an example). We keep "lesion" in the text. Page 13,14, 15, 16.

Reviewer B

This review discussed the clinical problems on the gastric ESD, especially regarding the risk factors or preventive methods for post-ESD bleeding.

Firstly, there are different forms of character in this manuscript. Second, the number of table or figure is too small. Third, most of the contents in this review are just the results in the previous reports. I hope the authors will describe and insist their suggestion or informative opinion more.

Reply:

1. The characters were unified.
2. The figure size was adjusted
3. As per the reviewer's comments, we summarized each section and gave our suggestions. Page 4, 5, 6, 11, 14, 16, 20, 21.